The Synthesis and Physical Properties of Some Cyclohexane Derivatives of Potential Biological Interest.

by

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SUMMARY

The historical development of analgetic drugs has been reviewed with respect to structural modifications of morphine, pethidine, methadone, morphinans and 6,7-benzomorphans. The development of analgetic receptor site theories has also been surveyed. A brief review of the application of Hansch-type analysis to structure-activity relationships has also been carried out.

Some basic derivatives of cyclohexane have been synthesised. The route consisted of a modification of the Strecker synthesis to yield an α-aminocyclohexylnitrile which was reduced to the corresponding primary amine using lithium aluminium hydride. The primary amine was benzoylated using several benzoylating agents.

The benzamides so produced were tested for CNS activity and several were found to have analgetic properties. Tentative relationships between structure and activity have been suggested.

A Hansch-type analysis of the structure-activity relationship of these benzamides was attempted. The parameters used in this analysis were pKa values, carbonyl stretching frequency values, calculated log P values and analgetic activity.

In order to compare their biological activity with the previously mentioned benzamides, an attempt was made to prepare some rigid analogues. The first route proposed was a ring closure, to form isoquinolones, of urethans derived from various α-amino-nitriles and α-aminoesters. The second route proposed was a ring expansion of 1-indanones to form isoquinolones.

Included in this study is an investigation into the course of a reaction between 2-bromo-2-methyl-1-indanone and diethylamine. It is also shown that 2-substituted-1-indanones yield, almost without exception, isoquinolones on ring expansion with hydrazoic

acid.

The 2-substituted-indanones and 3-substituted-isoquinolones prepared in this study were tested for potential CNS activity. Several of them were found to have analgetic properties and are being further investigated.

A brief consideration of the mass spectra of all the classes of compounds synthesised has been made and possible fragmentation pathways have been suggested.

To my parents

and Lyn.

ACKNOWLEDGEMENTS

I wish to express my thanks to Dr. G. B. A. Veitch and Professor D. G. Wibberley for their help, interest and encouragement during the course of this work.

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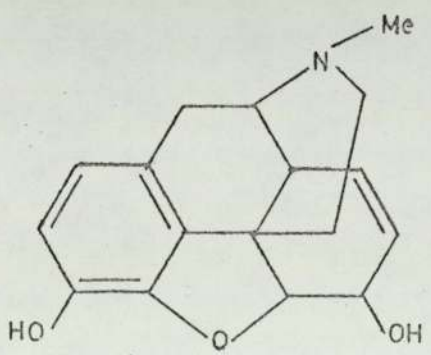
CONTENTS

SECTION I

A: A general survey of analgetics.

The properties of an ideal analgetic have been outlined by Pfeiffer[1] " It should be effective against all types of pain, but not alter the other sense receptors; it should have a large therapeutic margin of safety, a rapid onset and long duration of action. It should not depress the cardiovascular and respiratory systems; should not affect the gastro-intestinal tract, should be effective orally and parenterally; should not act as an anti-diuretic; should be inexpensive to manufacture and chemically stable; and should not lose its effectiveness through the development of tolerance which may in turn lead to habit formation or addiction." Although it is unlikely that this ideal substance is attainable man has sought this goal for many centuries.

Opium, the most ancient pain-relieving agent, was first used by the Assyrians who collected the opium poppy and extracted the crude drug. Opium was administered as an analgetic in this relatively impure form until 1803 when Sertuner isolated morphine (1).



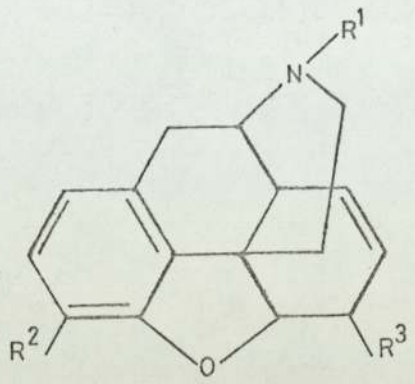
(1)

Another twenty-two alkaloids were subsequently isolated from opium, a number of which were clinically useful and it was upon the latter that the medicinal chemistry of the analgetics for the next 150 years was based.

The fact that the methylation of the phenolic hydroxyl group in morphine produced a compound with a marked decrease in the analgetic potency and dependence liability of the compound was the stimulus for the modification of the morphine molecule with a view to the separation of high analgetic potency and addiction liability. In 1929 the first systematic research programme was carried out by the National Research Council of the United States[2]. Over 450 compounds were prepared, 125 of them chemically derived from naturally-occurring alkaloids and the remainder synthetic compounds containing various portions of the morphine skeleton. The programme was not very successful as the most active derivative was only about one-tenth as active as codeine and was toxic. Since this programme many compounds have been synthesised by chemical modification of the morphine molecule. Relatively few have been successful and of those that were, heroin (2), dihydrocodeinone (3), oxymorphone (4), desomorphine (5) and metopon (6) are among the more important. More recently, interest in normorphine (7) was stimulated by the hypothesis that it may act as an intermediate in the mediation of analgesia, although this theory is not now generally accepted.

Since 1964 little work on novel morphine-like structures has been reported, although Bentley and co-workers[3,4] have carried out some interesting work on 6,14-endoethenotetrahydrothebaines (8).

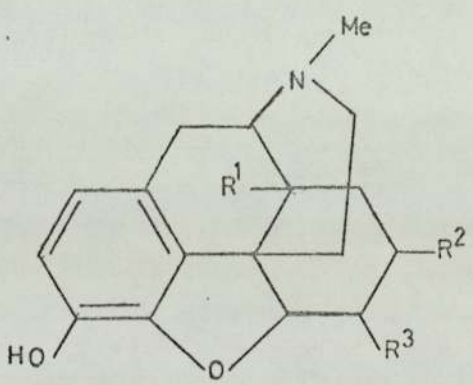
All the above compounds have rigid structures, but there is also a very important class of synthetic analgetics which has a greatly increased stereochemical flexibility. The initial work on these compounds was carried out by Eisleb and Schaumann[5], who, in 1939, prepared pethidine (9) which is still one of the most widely used substitutes for morphine. Many attempts have been made to modify the activity of the pethidine molecule. m-Hydroxylation of



(2) R^1 = Me, R^2 = R^3 = OCOMe.

(3) R^1 = Me, R^2 = OH, R^3 = =O.

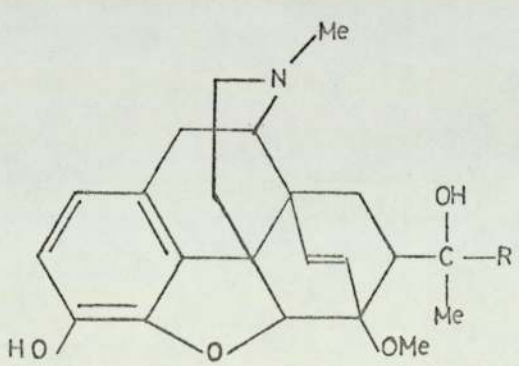
(7) R^1 = H, R^2 = R^3 = OH.



(4) R^1 = OH, R^2 = H, R^3 = =O.

(5) R^1 = R^2 = R^3 = H.

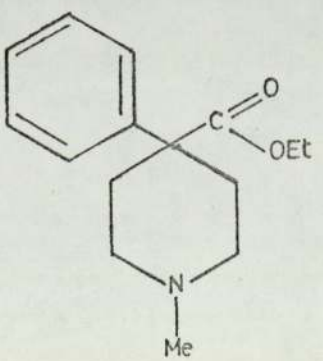
(6) R^1 = H, R^2 = Me, R^3 = =O.



(8)

the phenyl ring gave bemidone[6] which was no more active than pethidine. The ethyl ketone corresponding to this compound (ketobemidone (10)), however, was shown to be ten times as active as pethidine[7]. In 1943 the analgetic properties of 4-acyloxy-4-phenyl-1-methylpiperidines were reported[8] and it was also shown that compounds with the phenyl group in position 3, instead of position 4, (isopethidine (11)) were analgetically less active.

Between 1957 and 1962 a large number of structural variations of pethidine was reported. There was much investigation into variation of the N-substituent of pethidine. Perrine and Eddy[9] reported that the 1-phenethyl derivatives were two to three times as active as pethidine. During the next few years numerous N-substituted norpethidines were reported to have increased activity relative to pethidine, examples of the most active N-substituents being phenpropyl, p-aminophenethyl, p-amino-phenpropyl, p-nitrophenethyl, 4-pyridylphenethyl, cinnamyl and anilinoalkyl derivatives.



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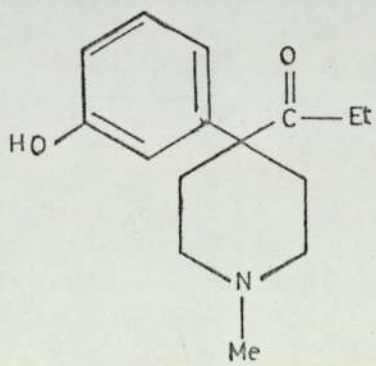

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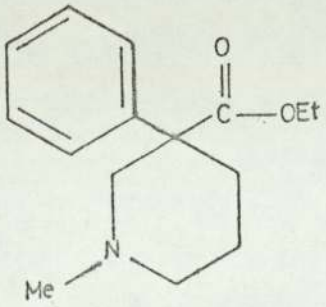
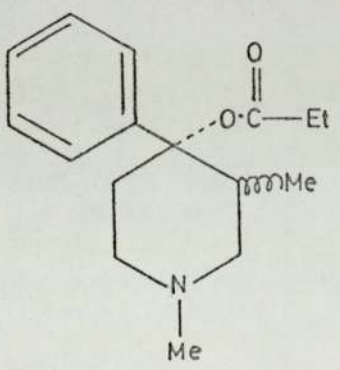


(11)

Much work has been carried out on the reversed esters of pethidine which, when substituted in the 3 position with a methyl group, gave rise to a diastereoisomeric pair of compounds, α- and β-prodine (12). α-prodine is approximately equal to morphine in analgetic potency and β-prodine is about three times as active as morphine. The structural variations applied to pethidine were also attempted on the prodine series of compounds and the resulting changes in analgetic potency were similar to those resulting from similar structural variations made in the pethidine series.

Although much work has been carried out since 1962 most of the progress has been in the area of structure-activity relationships and relatively few significant pethidine-type analgetics have been synthesised, with the exception of fentanyl[10] (13), which was shown to be 50 times as active as pethidine.



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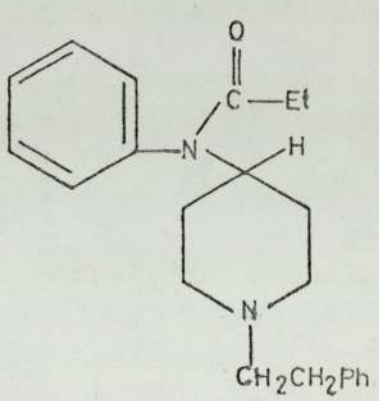


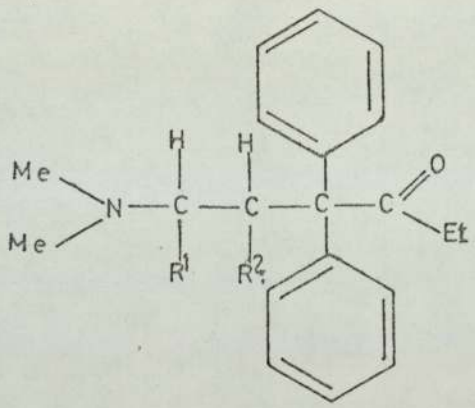
(13)

α- trans 4 Ph/3 Me

β- cis 4 Ph/3 Me

The development of a second major class of morphinomimetic analgetics, the diphenylpropylamines (14), was taking place at the same time as the development of the pethidines. The first of the series, methadone (14a), was introduced into medical use

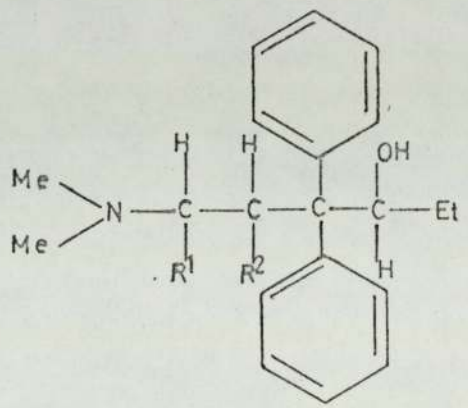
in 1946. Most structural analogues of methadone showed reduced activity compared to the parent compound or were inactive, although isomethadone (14b) is of comparable potency and replacement of the dimethylamino function by morpholino and piperidino produced phenadoxone and dipipanone respectively, both of which are clinically useful compounds. Replacement of the ketone function by hydroxyl gave rise to the methadol (15a)/ isomethadol (15b) series of compounds which were acetylated to yield the acetyl-methadols and -isomethadols.



(14)

(a) R^1 = Me, R^2 = H.

(b) R^1 = H, R^2 = Me.



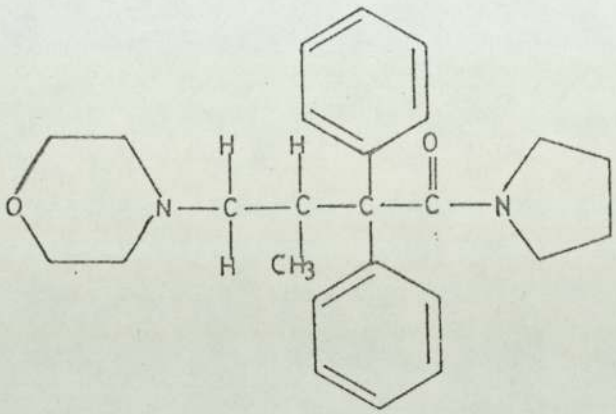
(15)

(a) R^1 = Me, R^2 = H.

(b) R^1 = H, R^2 = Me.

More recently the dextromoramide series of analgetics (16), in which the ethyl ketone group is replaced by a tertiary amide function, were produced by Janssen and Jageneau[11]. The compounds of this series were more potent than morphine but retained its side-effects and appeared to be of no clinical advantage. Replacement of the phenyl groups of methadone by thiophene rings

and introduction of an olefinic bond produced the dithienylbutenylamines[12] (17). Another group of analgetics, the discovery of which stemmed from the search for structural analogues of methadone, were the propoxyphenes (18).



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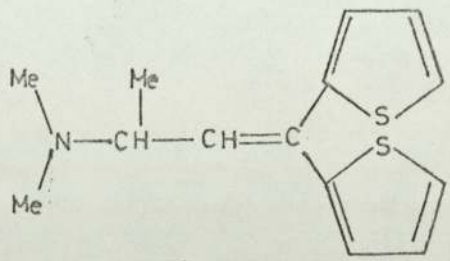

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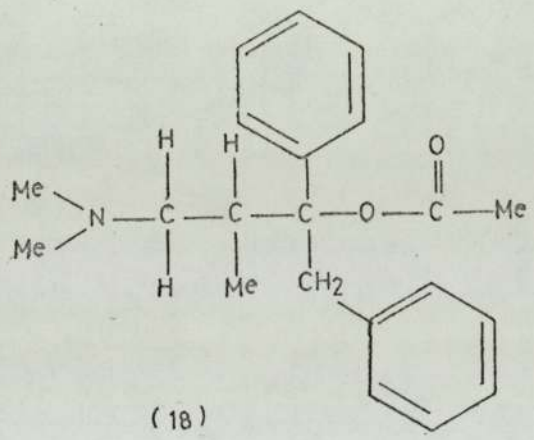
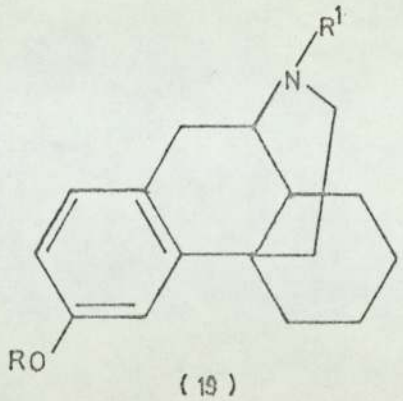


(18)

In addition, the morphinans (19), another class of analgetics, evolved from investigations of Grewe[13] in 1946 into the total synthesis of morphine. These compounds were regarded as 'simplified morphines' and resulted in the introduction of at least three clinically useful compounds. These were racemorphan (19a), its (-) isomer levorphanol and dextromorphan (19b). This latter compound was found to be almost devoid of analgetic activity but was a highly effective antitussive.

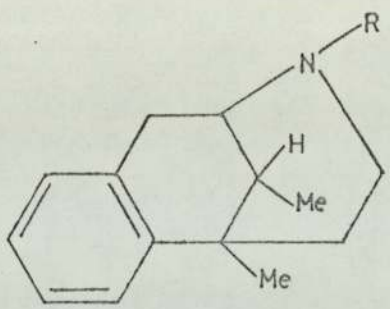
This simplification of the morphine structure was carried further by May[14], who synthesised 6,7-benzomorphans (20).



(19)

(a) R = H, R^1 = Me.

(b) R = Me, R^1 = Me.



(20)

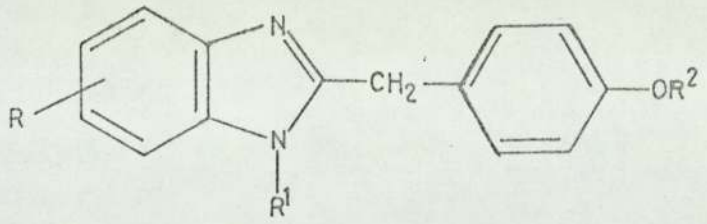
(a) R = CH_2-CH=C(Me)$_2$.

(b) R = Me.

(c) R = CH_2CH_2Ph.

This series of compounds proved to be the first in which a definite separation of analgetic potency and addiction liability was observed and, as such, was extremely important. The main clinically-used benzomorphans are pentazocine (20a), metazocine (20b) and phenazocine (20c) which are all narcotic antagonists to some extent.

There have also been a considerable number of apparently unrelated compounds which have proved to be analgetics. These include isoquinoline alkaloids and synthetic isoquinolines, diazabicyclo-octanes, methotrimeprazine, thiazolin-2-ones, 2-aminoindane and, probably the most important of these miscellaneous types, the benzimidazoles (21), discovered by Hoffman and co-workers[15,16].



(21)

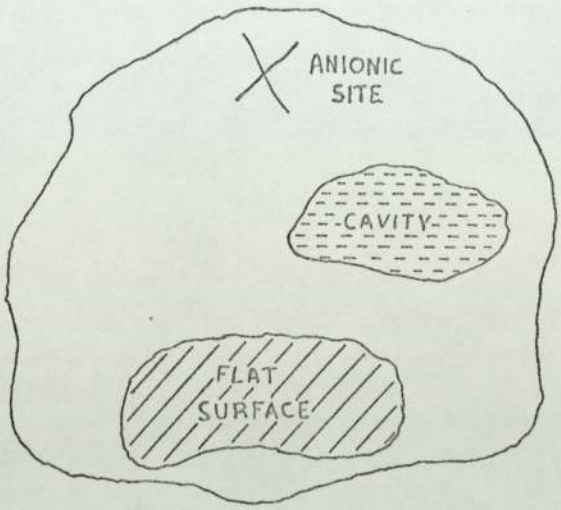
B: Structure-activity relationships.

The result of the research into the analgetic properties of partial structures of morphine was that early structure-activity relationship work was confined to an explanation of the analgetic activity of a compound in terms of its structural relation to the morphine molecule. When more flexible molecules such as pethidine were found to have activity, attempts were also made to relate these structures to morphine. However, as more analgetics were discovered, it became increasingly obvious that such rigid requirements could not be applied to all compounds and Beckett[17] in 1952 stated that " it appears probable from a consideration of the diverse types of compounds which have an analgetic activity equal to, or greater than, that of pethidine, that the minimum requirement for activity may be a hydrophobic group (or collection of groups) containing a basic centre with an optimum overall spacial arrangement".

Subsequently Beckett and Casy[18] investigated the stereochemical considerations of analgetic activity and proposed more elaborate requirements; namely, a basic centre ionised at physiological pH, a flat aromatic structure to allow bonding by van der Waals forces, a suitably positioned projecting hydrocarbon moiety and co-planarity between the basic centre and the flat aromatic surface. From these requirements Beckett and Casy proposed a receptor surface (22) and proceeded to attempt to relate all analgetic structures to this receptor surface. They had a considerable amount of success, being able to fit morphine-like structures, pethidine and related structures, dithienylbutenylamines and methadone and related structures to their postulated receptor surface.

In 1955, in a study sponsored by the World Health Organisation,

Braenden, Eddy and Halbach[19] enlarged on the features considered necessary for analgetic activity. After examining hundreds of

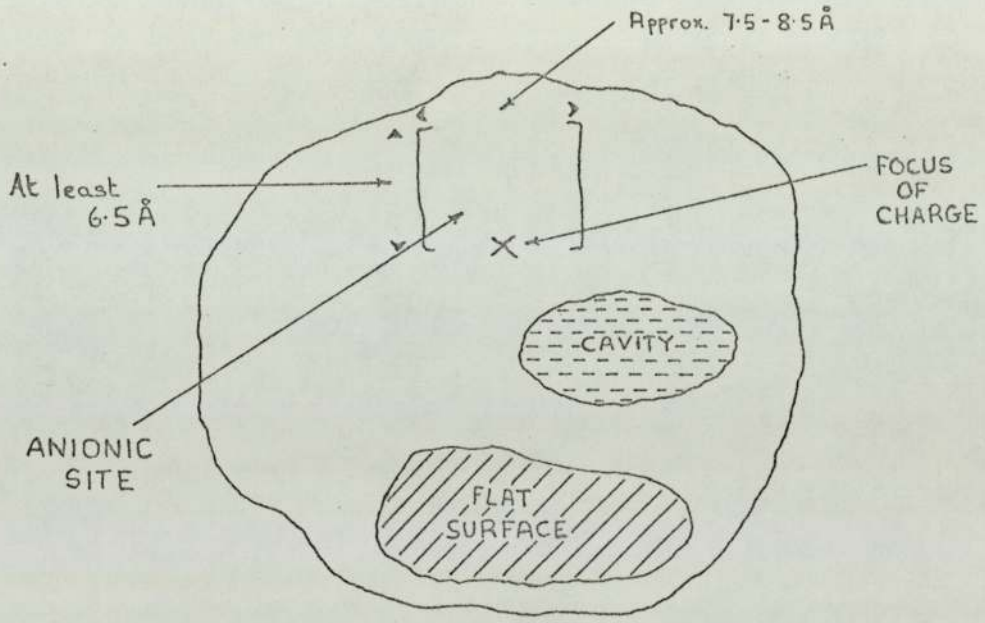


(22)

compounds they stated that the features necessary in compounds possessing morphine-like analgetic activity were a tertiary nitrogen (the group on the nitrogen being relatively small), a central carbon atom, none of whose valencies were connected with hydrogen, a phenyl group (or group isosteric with phenyl) which was connected to the central carbon atom and separation of the tertiary nitrogen from the central carbon atom by a two carbon chain.

In 1956 Beckett and co-workers[20] made extensive investigations into the cationic portion of analgetic molecules and the influence it might have on the binding of the drug to the receptor. Numerous dissociation constants were measured, including several series of methadone-type compounds, and it was shown that methadone-type molecules could adopt a conformation which would allow them easy association with the analgetic receptor, a situation which had

been previously unexplained. Beckett and co-workers then investigated factors contributing to the strength of attractive forces between the cationic site of the analgetic and the anionic site of the receptor. From a study of the variation of activity with the 'effective width' (minimum width consistent with free rotation of alkyl chains) of the basic group of several series of methadone-type compounds, a receptor which had a more specifically defined anionic site was proposed (23).



(23)

In 1959 Eddy[21] critically re-examined the features which had been considered essential for analgetic activity in 1955. The tertiary nitrogen was still an essential feature with only two or three compounds found to be active although not possessing a tertiary nitrogen. The statement that the group on the nitrogen should be relatively small was found not to hold as numerous compounds with large N-substituents had been shown to have high activity, for example, N-aralkyl derivatives of morphine and pethidine. The central carbon atom none of whose valencies were connected with hydrogen was found still to be essential,

although in 1955 it was believed that the carbon should be quaternary and this was shown not to be the case in the dithienylbutenylamines where the central carbon atom was attached to an olefinic double bond and was, therefore, only quasi-quaternary. A phenyl, or isosteric, group connected to the central carbon atom was found to be still an essential feature as was the two carbon chain between the central carbon and the tertiary nitrogen, although an exception to this feature arose with the discovery of the benzimidazole series of analgetics.

In 1962 Janssen[22] reviewed the chemical features associated with strong morphine-like activity. In the case of morphines he concluded that :

(a) stereochemistry was important,

(b) the features of the C ring were important,

(c) with the exception of heroin, variation of the aromatic ring produced loss of activity and

(d) the amine function must be tertiary, although the actual substituent was not so critical. In the case of the synthetic morphinans and 6,7-benzomorphans he concluded that the following features were essential for high activity :

(a) an L-shaped 3-ring skeleton,

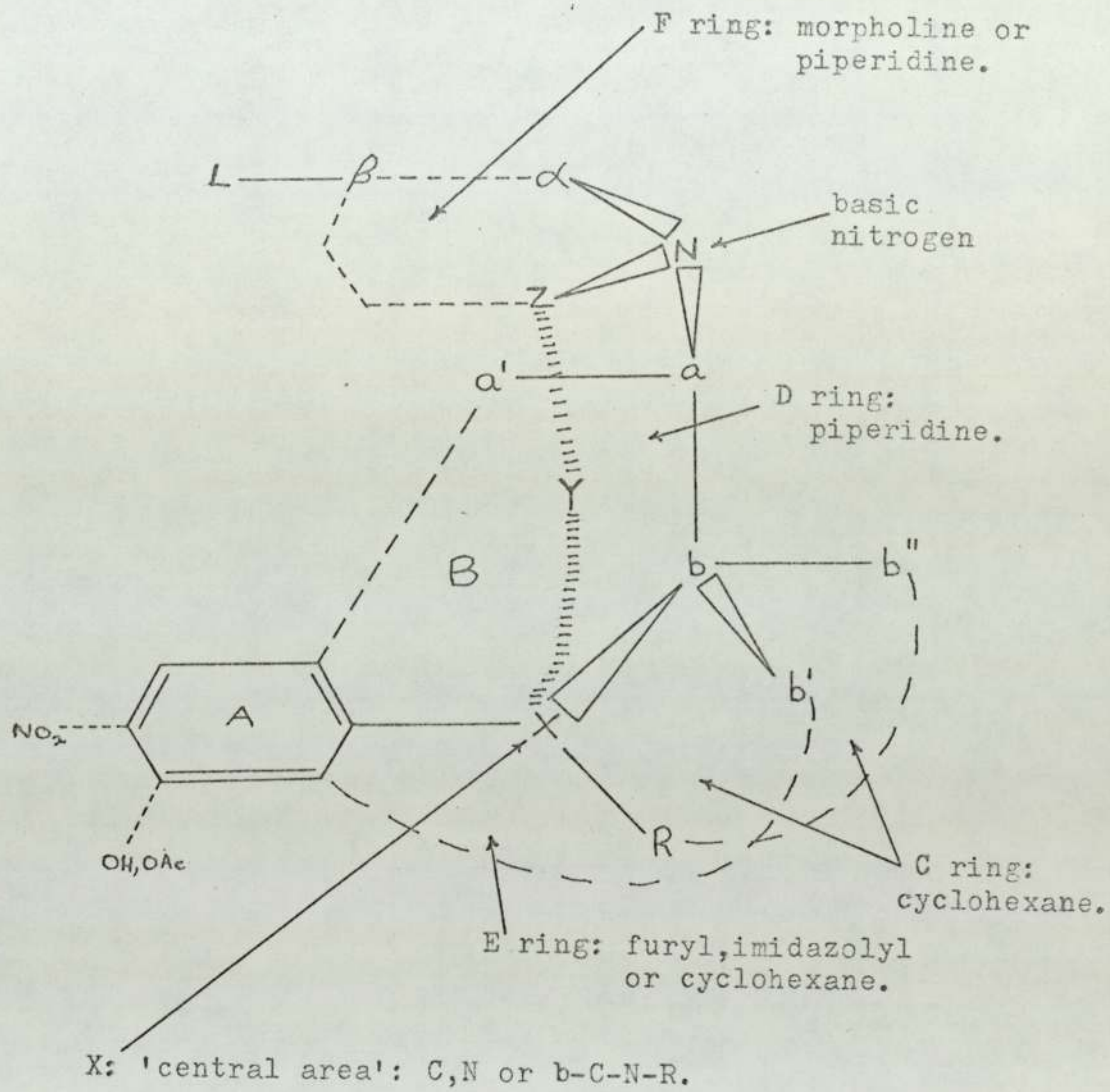
(b) a free or acetylated phenolic group,

(c) a tertiary nitrogen and

(d) at least two further substituents in the piperidine ring. In the case of the 4-phenylpiperidines the following features appeared to be essential for high activity :

(a) an unsubstituted phenyl nucleus attached to the ring nitrogen by an unbranched 3-carbon chain,

(b) a substituent of the type R-CH_2CH_2



(24)

L = phenyl or isosteric ring (L') connected to N as follows:

$L'CH_2\text{-}CH_2$, $L'CH_2\text{-}CH_2\text{-}CH_2$, $L'COCH_2\text{-}CH_2$, $L'CH(OH)CH_2\text{-}CH_2$, $L'NHCH_2\text{-}CH_2$,

$L'OCH_2\text{-}CH_2$, $L'CH{=}CHCH_2$, $L'C_6H_5CX\text{-}CH_2$, (X = CO.alkyl, CN.H) or L = H.

, , a, b, z are carbon atoms.

a', b', b'' are carbon or hydrogen atoms.

R represents lower alkyl, $OCOC_2H_5$ $COOC_2H_5$, $CHOCOCH_2C_2H_5$, COC_2H_5,

COC_3H_7, $CONMe_2$, $CONC_4H_8$, or $CCH_2C_6H_4p\text{-}OC_2H_5$.

(where R=OCO, COO or $COCH_2$) in position 4 of the piperidine ring and

(c) a suitable stereochemically arranged substituent at position 3 of the piperidine ring. Janssen then proposed a model structure (24) in which all the features discussed above were represented.

It became obvious, as more compounds were synthesised and found to have analgetic activity, that the receptor site requirements laid down by Beckett and Casy were inadequate. It became increasingly obvious that several aspects of structure-activity relationships in analgesia could not be explained by the Beckett and Casy model. For example, if the configurational selectivity of analgetic receptors towards compounds having an asymmetric centre in common with methadone (i.e. $R-CH_2-CH(CH_3)-B$) was examined, it was found that there was no consistent correlation between the configurations of the more analgetically active enantiomers (Table 1). Another feature not explained was the ability of identical N-substituents to produce compounds with either enhanced or diminished analgetic activity when attached to different molecules. For example, the replacement of the N-methyl group in pethidine by a cinnamyl moiety produced a compound whose activity was increased forty fold, whereas the same change in morphine produced a compound which showed a loss of potency.

In 1965 Portoghese[23] postulated that complex formation of different narcotic analgetics with receptors may involve differing modes of interaction, rather than a single type of drug-receptor interaction involving binding to the same site on the receptors. He presented three possible modes of interaction.

1. Interaction of different analgetics with a single species of receptor. This was subdivided into :

$R-CH_2-CH(CH_3)-B$		
R	B	Configuration of more active isomer
$Ph_2C-COEt$	NMe_2	R
$Ph_2C-COEt$	NC_4H_8O	R
Ph_2C-SO_2Et	NMe_2	R
$Ph_2C-COOEt$	NMe_2	S
$Ph_2C-CH(OH)Et$	NMe_2	S
$Ph_2C-CH(OAc)Et$	NMe_2	R
Ph-N-COEt	$N(Me)CH_2Ph$	S

Table 1.

(a) identical interaction - this had been previously assumed to be taking place and

(b) differing interaction in which the anionic site of the receptor was described as a pivotal point around which varying modes of binding could occur(25).

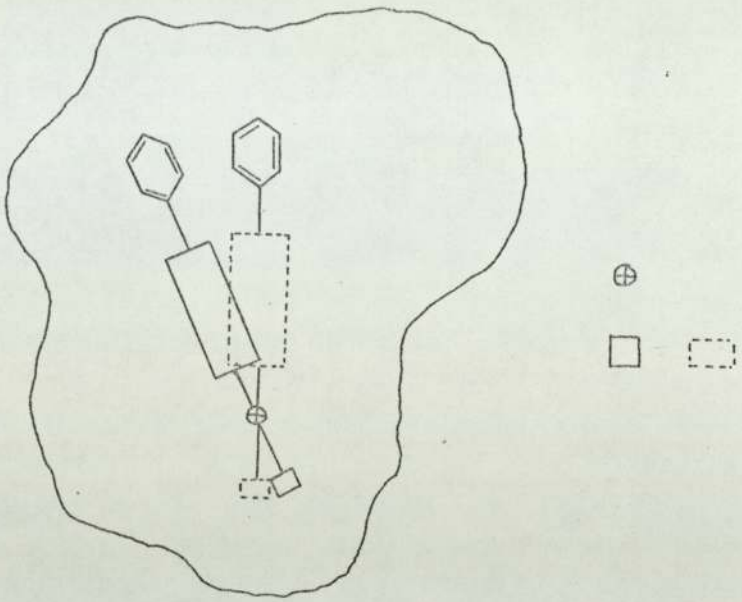
2. Interaction of different analgetics with two or more species of receptor common to the different analgetics. This was also subdivided into :

(a) identical partitioning on the receptors by different analgetics and

(b) dissimilar partitioning on the receptors by different analgetics. This situation could be explained by examination of the equations $A + \alpha + \beta \rightleftharpoons (A\alpha) + (A\beta)$ and $B + \alpha + \beta \rightleftharpoons (B\alpha) + (B\beta)$. Different analgetics (A and B) and species of receptor (α and β) common to A and B may interact so that the ratios $(A\alpha):(A\beta)$ and $(B\alpha):(B\beta)$ are similar (Case 2a.) or different (case 2b.).

3. Interaction of different analgetics with two or more species of receptor not common to the different analgetics. This case could be represented by the equations $A + \alpha + \beta \rightleftharpoons (A\alpha)$ and $B + \alpha + \beta \rightleftharpoons (B\beta)$ i.e. there could be a different receptor for each analgetic.

In 1968 Mautner[24] reviewed the whole area of the molecular basis of drug action and, in the field of analgetics, came to the conclusion that the whole concept of an analgetic receptor site would have to be completely re-evaluated. Although much work has been done on conformational studies in analgetics, these have been limited in that they provided evidence about the 'preferred' rather than the 'active' conformation, the two not necessarily the same except in the case of fully rigid molecules. Much work will have to be done to firmly establish the absolute configurations of rigid analgetics using X-ray crystallography and optical rotatory dispersion spectra, while a great deal of information will have to be gathered about the rotational barriers in flexible analgetic molecules. Progress has been made recently in studying the interaction of small ligand molecules with macromolecules (especially proteins) by the use of NMR[25] and it is possible that the same techniques may be applied to drug-receptor interactions. In addition advances in biochemical methodology and isolation of analgetic receptors in the central nervous system[26] may, in the near future, enable investigation of the receptor events mediating analgesia and this aspect is important, not only to our knowledge of pain mechanisms and their blockade, but also to the causes of tolerance and addiction to narcotic analgetics.



(25)

C: Hansch analysis.

An ability to predict the biological action of a given substance by virtue of its chemical constitution is one which is fundamental to our understanding of how drugs act and to the rational design of more effective analogues. The first attempt at such structure-activity correlation was the 'lipid hypothesis of narcosis' of Overton[27] and Meyer[28]. The hypothesis showed that the narcotic effect of a large number of chemically dissimilar substances increased with rising partition coefficient between a lipid and water, until lipid solubility became so great that the substance was insoluble in water, at which point activity began to decrease. The problem of the inapplicability of this hypothesis to substances administered in a gaseous form was solved by Ferguson[29]. He pointed out that as stable levels of narcosis were set up when an equilibrium existed between the concentration of the drug in the internal phase and its concentration in the phase in which biological activity occurred, simple thermodynamic principles could be applied. Thus he showed that the important parameter when considering correlation of narcotic activities was not the concentration of the substance in the applied phase, but its relative saturation.

In 1940 Hammett[30] derived an equation (26) which described the effect of m and p substituents on the rates of side-chain reactions of benzene derivatives.

$$\log \frac{K_x}{K_h} = \sigma\rho \text{---------} 26.$$

The equation was a linear relationship between the logarithims of the rate constants and the σ-values which were substituent constants independent of the reaction. ρ was defined as the reaction constant which was dependent only on the nature and

conditions of the reaction. It appeared possible that this type of equation could be used to predict biological activity and so, in 1962, Hansen[31] formulated a 'biological Hammett equation' based on a number of simplifying conditions. He used this equation to explain literature data on the inhibition of bacterial growth. At the same time, Zahradnik[32] found that the data for the magnitude of the biological effect of the members of an homologous series of aliphatic compounds of the type R-X could be correlated by means of equation (27).

$$\log \frac{T_i}{T_{Et}} = \alpha\beta \qquad \text{.....27.}$$

T_i denoted the molar concentration of the i-th member, and T_{Et} the molar concentration of the ethyl derivative, required to produce a specific effect. β was a constant characteristic of the substituent R and α characteristic of the biological system. It can be seen that the β constants of the Zahradnik equation were related to the σ constants of the Hansen equation.

A more mathematical approach to the structure-activity relationships was that of Free and Wilson[33] in which the structural changes per position were placed in order by estimating the amount of biological response attributed to each change. Singer and Purcell[34] reviewed the field of structure-activity models and concluded that they could be divided into two categories; firstly those in which the observed biological activity was expressed as a function of group contributions to the activity and, secondly, those based on linear free-energy relationships.

The most outstanding example of the second type was to be found in the work of Hansch and his colleagues who developed a basic equation from a study of the structure-activity relationships

in plant growth regulators[35]. Using a series of substituted phenoxyacetic acids, Hansch measured their partition coefficients (P) in an octanol/water system. A term π (= log P_x / P_h) was adopted, where P_x was the partition coefficient of the substituted compound and P_h that of the unsubstituted compound. A term log(1/C) was also used, where C was the concentration of compound necessary to elicit a specified response. Hansch then assumed that the molecules, given as a dose C, would make their way to the active site by a 'random walk' process with an effective concentration, AC, accumulating at the active site. Thus the rate of biological response could be expressed by equation (28), where K_x was the rate constant for the rate-limiting step in the 'random walk' process.

$$\frac{d(\text{response})}{dt} = ACK_x \qquad \text{---------- 28.}$$

Hansch then assumed a normal probability distribution, such that the probability of movement to the active site decreased exponentially with the square of differences between π and a constant ideal value, π_o . Therefore

$$A = f(\pi) = a \exp \left[- \frac{(\pi - \pi_o)^2}{b} \right] \qquad \text{-------- 29.}$$

where A = the probability of the molecule reaching the active site and a and b are constants. Substitution of A from equation (29) into equation (28) gave equation (30).

$$\frac{d(\text{response})}{dt} = a \exp \left[- \frac{(\pi - \pi_o)^2}{b} \right] CK_x \qquad \text{------ 30.}$$

Substitution of log(1/C) into equation (30), taking logarithms and collecting constants gave equation (31).

$$\log(1/C) = K\pi^2 + K'\pi\pi_o - K''\pi_o^2 + \log K_x + K''' \qquad 31.$$

Since π_o was a constant, and assuming K_x to be dependent on the substituent, the basic Hansch equation was evolved (equation 32).

$$\log(1/C) = K_1\pi - K_2\pi^2 + K_3\sigma + K_4 \text{ ------ } 32.$$

Having derived this equation, Hansch then attempted to evaluate the term π and to investigate any limitations the term might have. He determined partition coefficients between octanol and water for 203 mono- and di-substituted benzenes[36]. In this way he calculated π for 67 functional groups. On examination of the results he concluded that, although π varied from system to system, the variance for similar systems was not too great. Hansch also carried out similar work to determine values of π for aliphatic functions[37]. He then went on to apply this approach to some practical pharmaceutical problems. A study[38] on the localisation of substituted benzeneboronic acids in brain and tumour tissue in mice showed that localisation in the brain could be rationalised in terms of one parameter, π , whereas localisation in the tumour tissue depended on an additional electronic parameter, σ . After application of this technique to several series of congeneric drugs[39], he then applied the use of substituent constants and regression analysis to the study of enzymatic reaction mechanisms[40]. π was shown to be useful in establishing the stereospecific nature of hydrophobic bonding and a steric substituent constant, E_s, was introduced.

It had previously been stated[36,37] that the terms π and log P were additive and, in 1967, Hansch[41] published partition coefficient data on 54 organic compounds. He concluded that π and log P values appeared to be additive whenever there were no new effects in the summation which were not present in the constituent parts. The intramolecular interactions so far observed were electronic, hydrogen bonding and shielding effects. These shielding effects were divided into two types. Firstly, when two apolar groups were ortho to each other they would not have the same

number of structured water molecules around them as when they were para to each other. Secondly, shielding could occur by the folding of non-rigid molecules.

In 1968, more work by Hansch[41] showed that the hypnotic activity of groups of barbiturates depended almost entirely on their relative lipophilic character. The ideal lipophilic character was defined as log P_o and was of the order of 2 for the barbiturates, and it was shown that this was also the optimum value for many other sets of structurally unrelated hypnotics. Later in the same year it was discovered[42] that, in a study of metabolism of organic compounds, most of the variation in the structure-activity relationships appeared to be related to the relative lipophilic character of the compound and it was also found that many types of metabolic reactions had an ideal lipophilic character value of about 2.

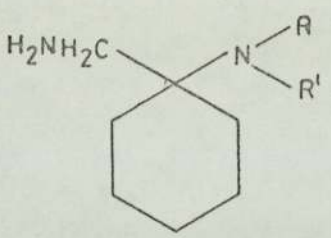
In 1969, Hansch[43], in a review of his own work, stated that his efforts had been directed towards the use of physical organic chemistry in an attempt to solve biochemical problems and that the evidence so far suggested that log P or π would make possible the use of computers in a numerical analysis of biochemical structure-activity problems. In the same year he took a further step towards solving the problems of drug-receptor interactions when he presented[44] a theoretical analysis of the passive penetration of drug molecules to their site of action in terms of their lipophilic character. This theory differed from those proposed for active transport because most drugs would not fit the highly specific biological transport mechanisms. The theory recognised that, in drug action, speed was essential and that in future, a knowledge of the optimum lipophilic character for a particular organ would shorten

the time required to develop an effective drug. More recently, criticism of the Hansch approach has been made by Higuchi and Davies[45]. They suggested that it could not cope with steric factors or metabolic inactivation processes too successfully and also that there are pitfalls in using multiple regression analysis techniques as a tool for interpreting biological data. They also suggested that the choice of parameters was often bewildering and that the more recent regression equations obtained were far too complex. Although, as yet, the literature contains few examples of predictions of high biological activity based on Hansch analysis being realised in practice, it is an attractive proposition that totally new chemical structures may be designed, having the same physico-chemical properties as predicted by Hansch analysis of a series of previously known active compounds.

SECTION II

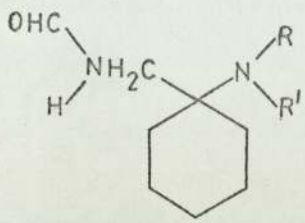
A: Benzamido derivatives of cyclohexyldimethylamine.

A number of diamino compounds have been reported to possess analgetic activity [46,47,48,49,50]. Some diamines of a simple nature have been synthesised[51] although these have not been tested for biological activity. These compounds (33), which are cyclohexyldiamines, were synthesised in order that the effect of formylation and methylation on analgetic activity could be examined.



(33)

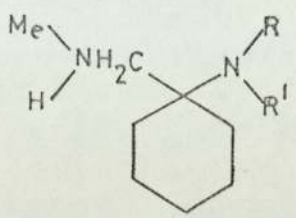
Formylation of the primary amine function of the cyclohexyldiamines renders the nitrogen virtually non-basic. Conversion of the added formyl group to a methyl group restores the dibasic nature of the molecule and it was thought that there might be a difference in analgetic activity between the monobasic and the dibasic compounds. Since the two most active compounds in the series (34 -45) were the N-formylmethylaminomethyl compound (40) and the N-methyl compound (39) no conclusion could be drawn as to the importance of the formyl group in relation to CNS activity in this series. However, these compounds do not contain an aromatic group and such a group is widely believed to be a necessity for analgetic activity. Thus, in a similar manner to formylation, the primary amine function could be made virtually non-basic by conversion to a benzamido function. Previous

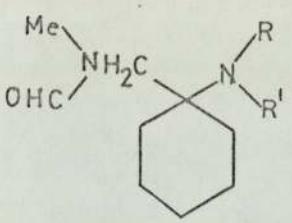


(34) NRR' = N^4-methylpiperazinyl (37)

(35) NRR' = dimethylamino (38)

(36) NRR' = piperidyl (39)

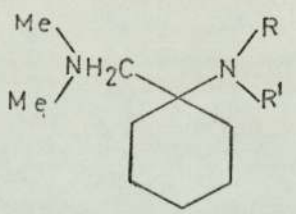




(40) NRR' = N^4-methylpiperazinyl (43)

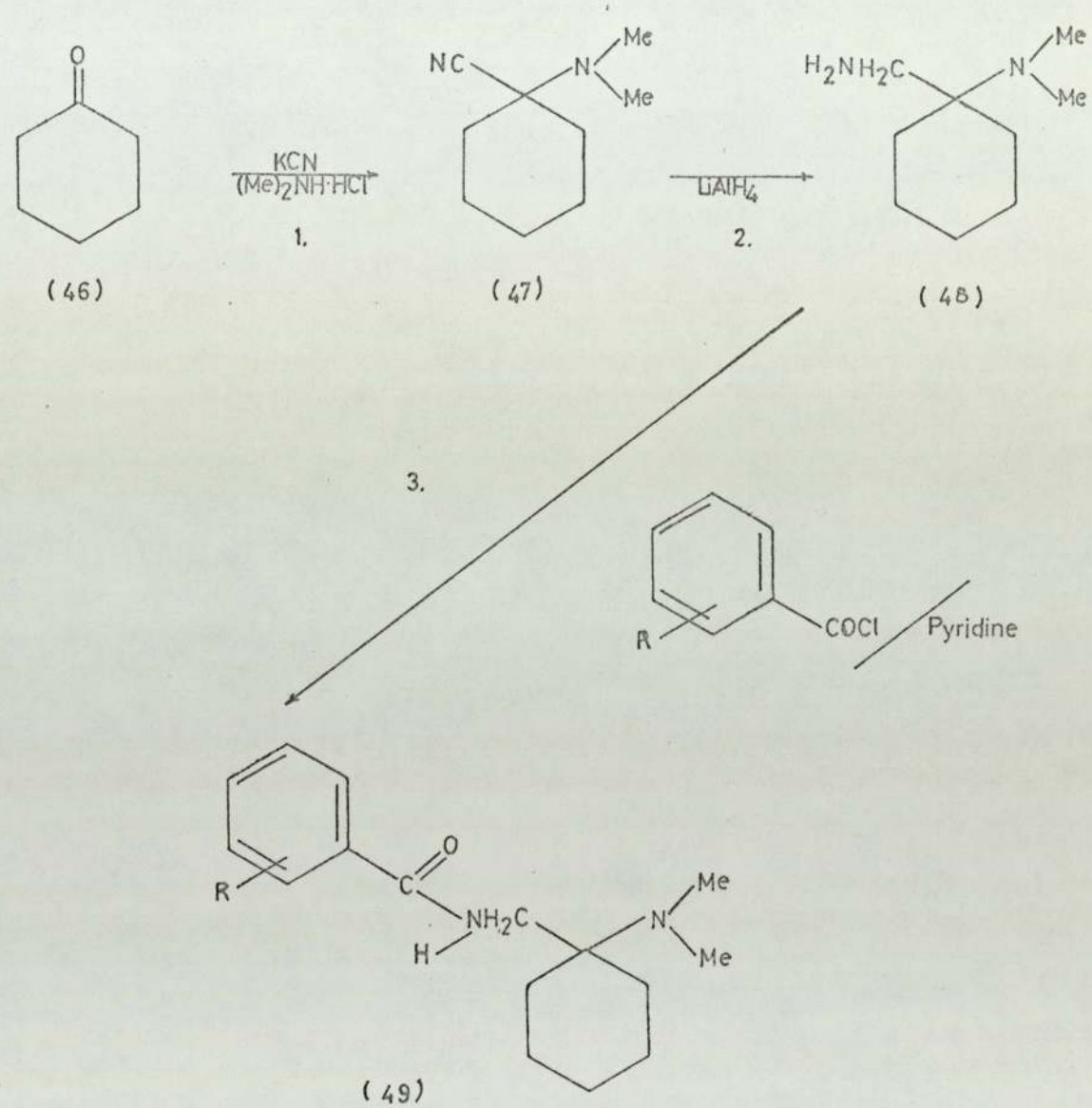
(41) NRR' = dimethylamino (44)

(42) NRR' = piperidyl (45)



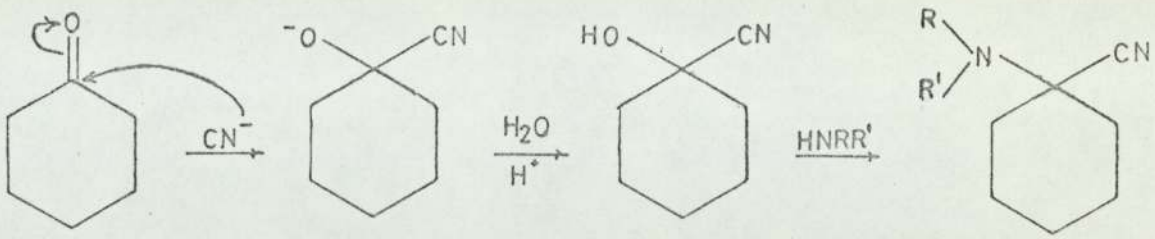
attempts[62,63] to produce analgetic activity by introduction of a benzamido group in another series of analgetics were, apparently, fairly successful and 3,4,5-trimethoxybenzoylmorphine and its 2-methyl derivative were found to have considerable tranquillising and analgetic effects, although a report in 1971[64] stated that, as a result of studies of analgetic potency and acute toxicity of substituted benzamides and anilides, benzamides were relatively inactive as analgetics.

The synthetic procedure adopted to obtain these benzamido derivatives (49) is shown in Scheme (1). Step 1 in Scheme (1) is a modification of the Strecker synthesis. The mechanism of the Strecker synthesis of α-aminonitriles is still in dispute. Two mechanisms are possible, first the formation of a cyanohydrin

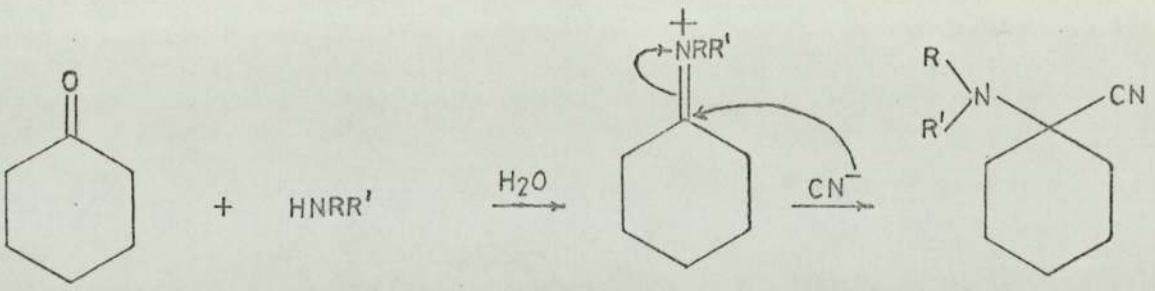


Scheme 1.

followed by S_N2 substitution by an amino group (Scheme (2)) and second addition of hydrogen cyanide to an intermediary amine (Scheme (3)). The second mechanism has gained much favour, however, since Ogata and Kawasaki[52] found that benzylideneaniline (50) reacted readily and quantitatively with hydrogen cyanide to give α-cyanobenzylaniline (51) while mandelonitrile (52) reacted slowly with aniline, giving rise to the suggestion that the



Scheme 2.



Scheme 3.

intermediate is benzylideneaniline or a Schiff base. Although the

$$Ar^1CH{=}NAr^2 + HCN \xrightarrow{\text{fast}} Ar^1CH\begin{matrix}NHAr^2\\CN\end{matrix}$$

(50) (51)

$$Ar^1CH(CN)OH + Ar^2NH_2 \xrightarrow{\text{slow}} Ar^1CH\begin{matrix}NHAr^2\\CN\end{matrix}$$

(52) (51)

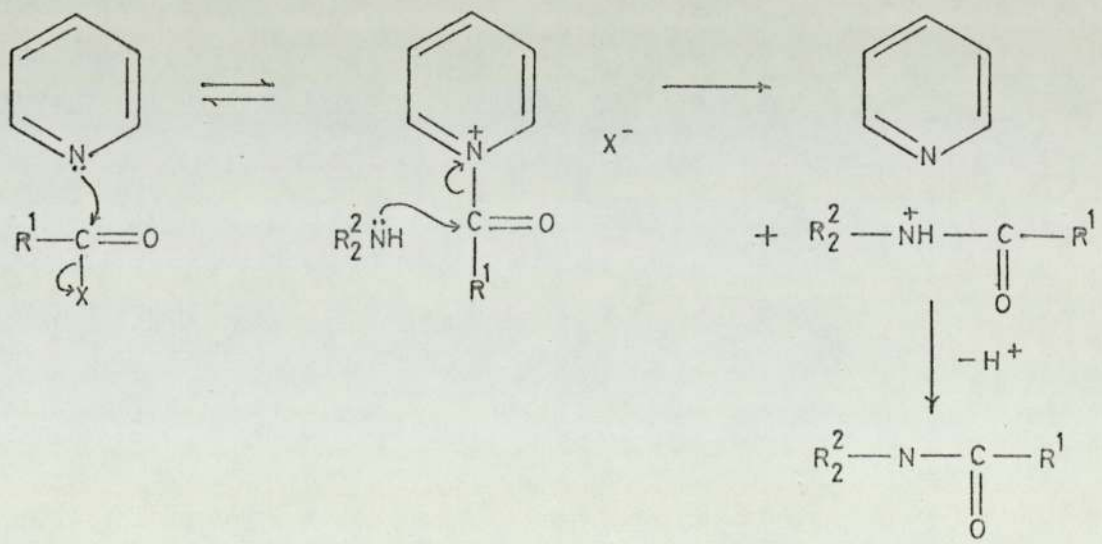
α-aminonitrile (47) had been synthesised previously[51] the synthetic procedure used produced only an oil in 62% yield. A change in the reaction conditions, from refluxing 24hr. in 50% ethanol to stirring for 24hr. at room temperature in aqueous solution, increased the yield to 80% and also increased the

purity of the final product sufficiently for it to form a colourless solid.

Step 2 in Scheme (1) is a reduction of the α-aminonitrile (47) to the diamine (48) using lithium aluminium hydride. This reaction had been carried out previously in good yields[51] and the same technique was used in this study.

Step 3 in Scheme (1) was reaction of the amine (48) with the appropriately substituted benzoyl chloride in the presence of pyridine.

Three of the benzamide series of compounds had previously been prepared[51] and the method used for the synthesis of these three compounds was adopted as the basic synthetic procedure for the whole series. The reaction mechanism is thought to involve the formation of an acylpyridinium salt by reaction of pyridine with the acyl halide. This salt then reacts with the amine to yield the desired product (Scheme (4)). Electron-repelling groups in the



Scheme 4.

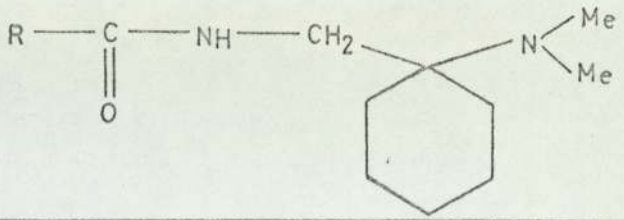
acid chloride are known[53] to decrease the electrophilicity and this makes the reaction more difficult. A number of the compounds

to be prepared contained an electron-repelling substituent in the benzene ring e.g. 2-methoxy, 4-methoxy, 4-dimethylamino, 4-methyl, 4-ethoxy, 3,4-dimethoxy, 3,4,5-trimethoxy, but practical difficulties were only encountered in the case of the 3,4,5-trimethoxy compound (49, R=3,4,5-trimethoxy). In this case, instead of the normal reaction conditions (standing at room temperature for 1hr.), the reaction mixture had to be refluxed for 8hr. in order to give a reasonable yield of the required product. All the reactions were carried out in dry pyridine. This was because of the necessity, when using weakly nucleophilic amines, to remove the hydrochloric acid produced, in order to obtain a reasonable yield of the amide.

Most of these benzamido derivatives were submitted for primary CNS screening and the detailed results appear in the pharmacology section (Table (16)). Table 2 shows a simplified version of the qualitative results of the primary screen. In the mouse hot-plate test all the compounds showed some degree of activity, although in the case of the 4-nitro (58) and the 4-O-ethoxyformyl (65) compounds this was very slight. All the other compounds tested showed 100% inhibition of the reflex response in the mouse hot-plate test. When the compounds were tested in the phenylquinone-induced writhing test, which is another primary screening test for analgesia, the activities obtained were not as good. Several compounds showed no activity in this test, these being the 4-nitro (58), 2-methoxy (59), 4-methoxy (61), β-naphthyl (62), 4-O-ethoxyformyl (65) and the 3,4-dichloro-cinnamoyl (66) derivatives.

The unsubstituted benzamide (53) showed only moderate activity which compared unfavourably with aspirin. The 4-fluoro (54) and the 3,4-dichloro (55) compounds both showed marked activity which was an improvement on that of aspirin. Three other compounds also

TABLE 2.



COMPOUND	BEHAVIOUR IN THE MOUSE	DIRECT HOT PLATE TEST	EFFECT ON PHENYL QUINONE INDUCED WRITHING
✳(53)	MODERATE ACTIVITY. STRAUB TAIL.	MARKED ACTIVITY, 100% INHIBITION.	MODERATE ACTIVITY, < ASPIRIN.
✳(54)	REDUCED RESPONSE TO PAIN.	MARKED ACTIVITY, 100% INHIBITION.	MARKED ACTIVITY, ≫ ASPIRIN.
✳(55)	REDUCED RESPONSE TO PAIN.	MARKED ACTIVITY, 100% INHIBITION.	MARKED ACTIVITY, ≫ ASPIRIN.
(56)	NO RESULT AVAILABLE.	MARKED ACTIVITY, 100% INHIBITION.	MODERATE ACTIVITY.
✳(57)	INACTIVE.	MARKED ACTIVITY, 100% INHIBITION.	MARKED ACTIVITY, ≏ CODEINE.
(58)	NEGLIGIBLE ACTIVITY. HIGH POSTURE.	NEGLIGIBLE ACTIVITY.	INACTIVE.
(59)	INACTIVE.	MARKED ACTIVITY, 100% INHIBITION.	INACTIVE.
✳(60)	NO RESULT AVAILABLE.	MARKED ACTIVITY, 100% INHIBITION.	MARKED ACTIVITY.
(61)	NEGLIGIBLE ACTIVITY. LOW POSTURE.	MARKED ACTIVITY, 100% INHIBITION.	INACTIVE.
(62)	NEGLIGIBLE ACTIVITY. LIMB SPLAY. STRAUB TAIL.	MARKED ACTIVITY, 100% INHIBITION.	INACTIVE.
✳(63)	MODERATE ACTIVITY. STRAUB TAIL. RAISED POSTURE. INHIBITION OF PAIN RESPONSE.	MARKED ACTIVITY, 100% INHIBITION.	MARKED ACTIVITY, > CODEINE (WRITHING ABOLISHED).
✳(64)	NEGLIGIBLE ACTIVITY. STRAUB TAIL.	MARKED ACTIVITY, 100% INHIBITION.	MARKED ACTIVITY, > CODEINE (WRITHING ALMOST ABOLISHED).
(65)	NEGLIGIBLE ACTIVITY. STRAUB TAIL. RAISED POSTURE.	MODERATE ACTIVITY.	INACTIVE.
(66)	NEGLIGIBLE ACTIVITY. LIMB SPLAY.	MARKED ACTIVITY, 100% INHIBITION.	INACTIVE.

TABLE 2 (CONT).

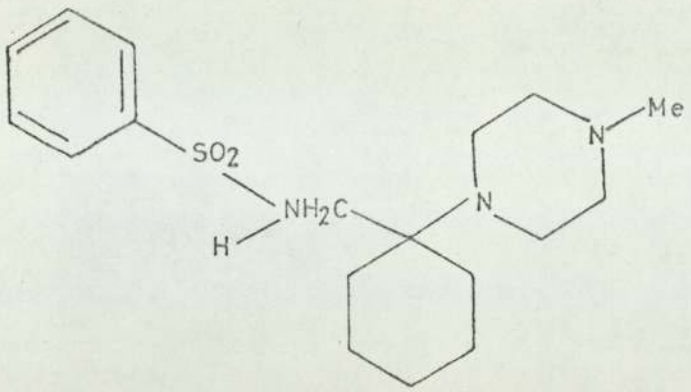
(53) R = phenyl.
(54) R = 4-fluorophenyl.
(55) R = 3,4-dichlorophenyl.
(56) R = 2-chlorophenyl.
(57) R = cinnamyl.
(58) R = 4-nitrophenyl.
(59) R = 2-methoxyphenyl.
(60) R = 4-chlorophenyl.
(61) R = 4-methoxyphenyl.
(62) R = 2-naphthyl.
(63) R = 4-bromophenyl.
(64) R = 3-bromophenyl.
(65) R = 4-O-ethoxyformylphenyl.
(66) R = 3,4-dichlorocinnamyl.

showed marked activity in the phenylquinone induced writhing test. The cinnamamide (57) had an activity approximately equal to that of codeine, the 4-bromobenzamide (63) had an activity greater than codeine, completely abolishing the writhing and the 3-bromobenzamide (64) also had an activity greater than that of codeine, although in this case writhing was not quite totally abolished.

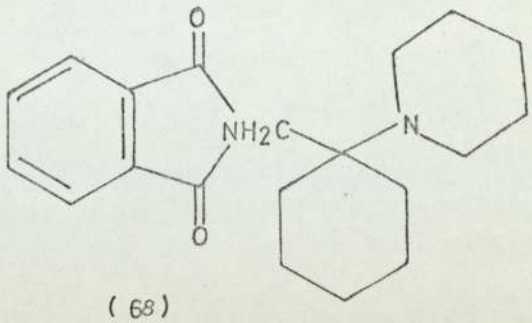
Of the compounds found active in the primary pharmacological screen, seven were investigated further (the compounds marked * in Table 2). It can be seen that the compounds which show the highest analgetic activity are those which contain one or more halogen substituents on the benzene ring. Compounds which also show reasonably high activity are the unsubstituted benzamide (53) and the unsubstituted cinnamamide (57). Although the order of increasing ED_{50} values (see Pharmacology section) for these seven compounds varies in the phenylquinone induced writhing test and the hot-plate test, the overall range of the values obtained is not large enough to enable any significance to be placed on these differences in order.

If the 3,4-dichloro derivative (55) is considered to be the structure associated with optimum activity in the compounds of this benzamide series to date, it appears that any structural variation of this molecule leads to compounds which have reduced analgetic activities. Replacement of the halogen substituent on

the benzene ring by any other substituent produces compounds in which the analgetic activity is reduced, or in some cases, totally abolished. It is interesting, however, that activity is retained by the cinnamyl derivative (57), although the 3,4-dichlorocinnamyl derivative (66) shows no activity in the phenylquinone induced writhing test. Although almost all the compounds show 100% inhibition of the response in the hot-plate test, this test is not a true indication of analgetic activity, only one of general CNS depressant activity and so too much weight should not be placed on any results obtained in this test. Variation of the basic group of compound (53) also produces compounds with reduced analgetic activity. Replacement of the dimethylamino group by piperidino gives rise to a compound which shows no activity and by $\underline{N}^4$-methyl-piperazino to a compound with reduced analgetic activity. The amide bond of the unsubstituted compound (53) also appears to be an essential feature of a compound with high activity; reduction of the carbonyl group produces the corresponding alcohol which has reduced activity in the hot-plate test and is inactive in the phenylquinone test. Similarly, if the amide group is replaced by a sulphonamide (67) or phthalimide (68) function, the analgetic activity of the compounds is totally abolished. It can be seen that a change in the functional groups of the molecule (53) leads to a compound with an altered activity, but it is also known that, if the cyclohexyl portion of the molecule is replaced by alkyl groups, compounds with reduced activity and increased toxicity are produced. A change in the type of biological activity of the compound is brought about if the cyclohexyl portion is replaced by hydrogens. A large number of substituted benzamides of the type (69) have been synthesised and found to have various biological properties including local anaesthetic activity[54,55,56,57,58]



(67)



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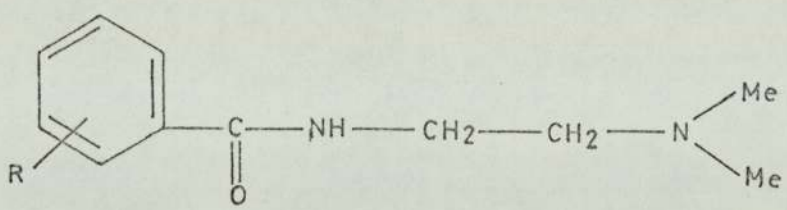


(69)

anti-tussive properties[59], anti-arrhythmic activity[60] and CNS depressant properties[61].

This last kind of activity is interesting as one of the benzamides (59) showed CNS depressant activity in the primary pharmacological screen. In a secondary psychopharmacological screen compound (59) was found to give 58% inhibition of the reaction of hyper-reactive rats at a dose of 25mg/Kg of body weight. The compound, however, had no effect on conditioned suppression at a dose of 30mg/Kg subcutaneously and thus, although possessing a certain amount of anti-anxiety activity, was of no further interest.

B: Hansch analysis of benzamide derivatives.

The Hansch analysis approach has been applied to many biomedicinal systems. Structure-activity relationships have been examined in such series of compounds as substituted phenoxyacetic acids[65], penicillins[66], benzoic acids[67], sulphanilamides[68] and benzeneboronic acids[38].

The first attempt at a Hansch analysis approach to structure-activity relationships in analgesia was made by Portoghese in 1965[69], when he investigated a number of N-substituted phenylpiperidine derivatives. He postulated that, if two different series of analgetics were exerting their effect at the same receptor site, identical changes of a portion of the molecule in each series should produce parallel variation in activity. If a point is plotted whose abscissa is the logarithm of the activity for the substituted compound in one series and whose ordinate is the logarithm of the activity of the identically substituted compound in the other series the resultant points should fall on a straight line. If the binding modes of the two series are the same, the slope of the regression line should be of the order of unity, assuming that the substituent had an identical effect on the biodistribution of both series.

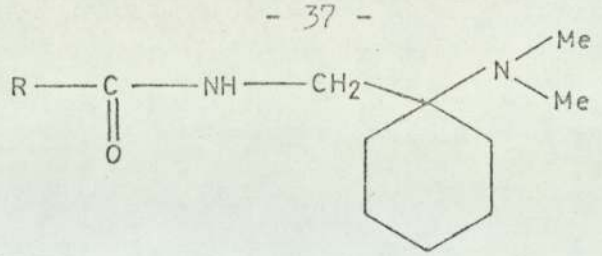
Since this attempt by Portoghese little work has been published on Hansch analysis of structure-activity relationships in analgesia. Thus, having synthesised a series of analgetically active benzamide derivatives of cyclohexyldimethylamine, it was decided to attempt an analysis of the structure-activity relationships in this series.

Although little work has been done on benzamides with analgetic activity, a number of benzamides showing other biological properties have been examined. An examination[70] into

the correlation of in vitro sulphonamide activity with pKa and Hammett values included a study of a series of N-benzoyl-sulphanilamides. More recently a study[71] on the electronic, hydrophobic and steric effects of binding of inhibitors to horse liver dehydrogenase-reduced pyridine coenzyme binary complex included regression analysis on the structure-activity relationships of a series of m- and p-substituted benzamides.

When choosing parameters for attempts at quantitative analysis it is important to consider which structural features of the drug molecule may be important in any structure-activity relationship. In the case of analgetics it has long been thought that the basic group plays an important role in drug-receptor interactions. The first study of the basic group in analgetics was in 1941[72] when Oberst and Andrews examined the electrolytic dissociation of morphine derivatives and certain synthetic analgetic compounds. They came to the conclusion that there was no correlation between the analgetic and toxic properties of the drugs and the values of the dissociation constants of the basic centres in the molecules. Similarly, in 1956, Beckett[20a] came to the conclusion that there was no simple relation between dissociation constants and analgetic activities. The only conclusion drawn was that, as all the pKa values lay within the range 7.8 - 8.9, it appeared probable that the basic group was ionised at physiological pH to allow association with the anionic site of the analgetic receptor. Thus it was decided that one parameter which should be used in a Hansch analysis of the series of benzamides was their pKa values, which are representative of the effect of the basic part of each molecule.

The method used for the determination of the pKa values was that recommended by Albert and Sergeant[73] and the values obtained



COMPOUND	pKa
R = phenyl	8.28
R = 4-fluorophenyl	8.52
R = 3,4-dichlorophenyl	8.36
R = 2-chlorophenyl	8.43
R = cinnamyl	7.21
R = 4-nitrophenyl	8.38
R = 2-methoxyphenyl	8.57
R = 4-chlorophenyl	8.30
R = 4-methoxyphenyl	9.37
R = 2-naphthyl	8.34
R = 4-bromophenyl	8.22
R = 3-bromophenyl	8.40
R = 4-tolyl	8.25
R = 3,4,5-trimethoxyphenyl	8.63
R = 4-ethoxyphenyl	8.81

Table 3.

are listed in Table 3. The pKa values were inserted as data, together with the ED_{50} values which were available, in a computer programme designed to perform regression analysis on sets of data. This procedure was carried out for ED_{50} values in both the hot-plate and phenylquinone tests, and the respective equations (70) and (71) were produced.

$$BA = -20.6(12.7)pKa + 184.5; \quad n = 6, \quad r = 0.63 \qquad (70)$$

$$BA = 101.0(129.5)pKa - 817.7; \quad n = 7, \quad r = 0.28 \qquad (71)$$

BA represents biological activity (in terms of ED_{50} values).

n = number of observations.

r = correlation coefficient.

It can be seen from the equations (70 and 71) that there is no simple correlation between pKa and analgetic activity, although the correlation is slightly better in the hot-plate test, r = 0.63 compared with r = 0.28. However, this is probably due to the small number of observations (only 6) in this analysis. In the above analysis the biological activity is represented by ED_{50}

values. However, it is a known technique in Hansch analysis to represent the biological activity by a term log(1/C) where C = the concentration necessary to produce a specific biological response e.g. an ED_{50} value. Thus, if log(1/C) is plotted against pKa values for both the hot-plate and the phenylquinone tests, the following equations are obtained.

$$\log(1/C) = 0.547(0.417)pKa - 5.30; \quad n = 6, \quad r = 0.59 \qquad (72)$$

$$\log(1/C) = -0.183(0.408)pKa + 0.79; \quad n = 7, \quad r = 0.20 \qquad (73)$$

Correlation between log(1/C) and pKa values appears to be slightly worse than a straight correlation between ED_{50} values and pKa values.

Another part of a drug molecule which is considered important in analgetic activity is the phenyl ring which, it is postulated, can aid drug-receptor interaction by the formation of hydrophobic bonds. If this is indeed the case, then a variation in the electron density of the phenyl ring could possibly alter the degree of interaction taking place. In the benzamide series of compounds the electron density of the phenyl ring is varied by the presence of different substituents. A convenient method of measuring the effect of these substituents would be to study the carbonyl stretching frequency, with which the ring substituents are known to have a Hammett-type relationship[74]. Thus the carbonyl stretching frequencies in the solid state were measured accurately (Table 4) and an attempt was made to relate the results obtained to biological activity. The regression equations for the hot-plate test (74) and the phenylquinone test (75) were obtained.

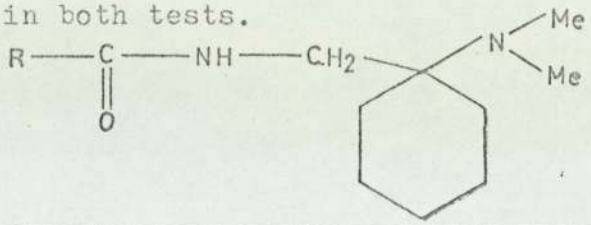
$$BA = -0.304(0.252)\,\sigma^{+} + 512; \quad n = 6, \quad r = 0.52 \qquad (74)$$

$$BA = 0.161(0.395)\,\sigma^{+} - 223; \quad n = 7, \quad r = 0.18 \qquad (75)$$

where σ^{+} is the parameter representative of the carbonyl stretching frequency.

Also plotted against the measured carbonyl frequencies was log(1/C)

obtained in both tests.



COMPOUND	CARBONYL FREQUENCY cm^{-1}
R = phenyl	1639
R = 4-fluorophenyl	1653
R = 3,4-dichlorophenyl	1676
R = 2-chlorophenyl	1656
R = 3,4,5-trimethoxyphenyl	1665
R = cinnamyl	1653
R = 4-nitrophenyl	1649
R = 2-methoxyphenyl	1628
R = 4-chlorophenyl	1626
R = 4-methoxyphenyl	1656
R = 2-naphthyl	1656
R = 4-bromophenyl	1657
R = 3-bromophenyl	1643
R = 4-tolyl	1639
R = 4-ethoxyphenyl	1655

Table 4.

Again the respective regression equations for the hot-plate (76) and phenylquinone (77) tests were obtained.

$$\log(1/C) = 0.009(0.018)\,\sigma^{+} - 15.1; \quad n = 6,\ r = 0.23 \qquad (76)$$

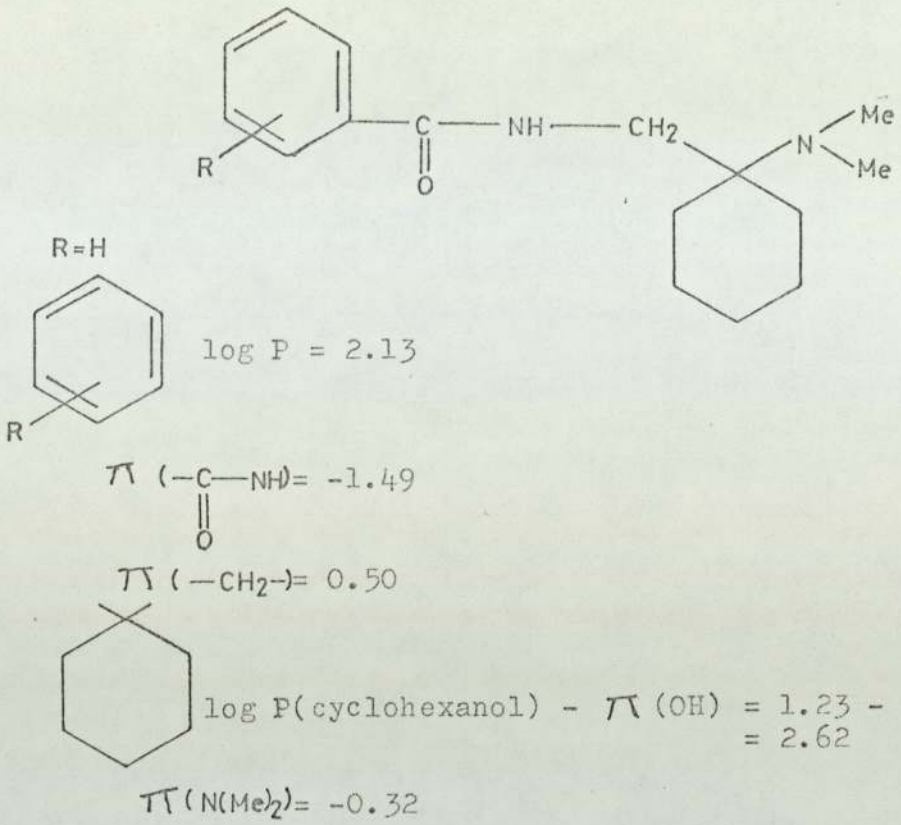
$$\log(1/C) = 0.021(0.007)\,\sigma^{+} - 34.9; \quad n = 7,\ r = 0.80 \qquad (77)$$

In the cases of equations (74), (75) and (76) there is very poor correlation. In equation (77), however, the correlation is approaching a reasonable level. The correlation coefficient is 0.8, which means that 64% of the biological activity could be explained by the parameter σ^{+}. An application of a T-statistical test to the regression equation (77) gave a value of T = 2.93, compared with a value of T = 4.03 necessary for significance in a regression analysis with 5 'degrees of freedom'. Thus it can be seen that, as with pKa values, there appears to be no simple correlation between analgetic activity and the electron density

of the phenyl ring, assuming the carbonyl stretching frequency to be a proportional measure of the electron density.

One of the most used parameters in Hansch analysis is log P. Log P represents the logarithm of the partition coefficient between octanol and water of the molecule being studied. Log P is usually used in a Hansch analysis of a series of compounds acting in a complex system which may include transport, serum-binding and receptor-binding factors. Log P has been used in a large number of studies of biologically active molecules e.g. barbiturates[75], hypnotics[41], antifungal agents[76] and antibacterials[77]. In the field of analgetics, an investigation[78] into a series of p-substituted acetanilides showed that buccal absorption of the compounds was related parabolically to analgetic activity and that the correlation was slightly better than that between log P and analgetic activity.

Since the actual physical measurement of the partition coefficients of a number of molecules is both lengthy and tedious, and taking into account the fact that log P has been shown to be an additive-constitutive property of a molecule[36,37,79], it was decided to use calculated values of log P for the purpose of this study. The method of calculation used was that the molecule was considered in parts and the relevant log P values for each part were summated. Although it is possible to divide the molecule in several different ways, if the same divisions are used throughout the series, then the values obtained should be comparable as a series. If the molecule is divided into parts as in Scheme 5, then the calculated log P values obtained are as in Table 5.



calculated log P = 2.13 + (-1.49) + 0.50 + 2.62 + (-0.32)
= 3.44

Scheme 5.

COMPOUND	log P
R = phenyl	3.44
R = 4-fluorophenyl	3.58
R = 3,4-dichlorophenyl	4.86
R = cinnamyl	4.14
R = 4-chlorophenyl	4.15
R = 4-bromophenyl	4.30
R = 3-bromophenyl	4.30

Table 5.

The calculated log P values were plotted against analgetic activity in the hot-plate and phenylquinone tests and the respective regression equations produced (78,79) were:

$$BA = -8.09(6.08)\log P + 42.7; \quad n = 6, \; r = 0.55 \qquad (78)$$

$$BA = -81.3(56.5)\log P + 373; \quad n = 7, \; r = 0.54 \qquad (79)$$

Also plotted against the calculated log P values was log (1/C)

and the respective regression equations for the hot-plate (80) and the phenylquinone (81) tests were:

$$\log (1/C) = 0.565(0.359)\log P - 3.13; \quad n = 6, r = 0.62 \qquad (80)$$

$$\log (1/C) = 0.595(0.277)\log P - 3.16; \quad n = 7, r = 0.69 \qquad (81)$$

In all four equations (78,79,80,81) the level of correlation is not particularly good and again no conclusion can be drawn as to the relationship between the calculated value of log P and analgetic activity in this series of compounds.

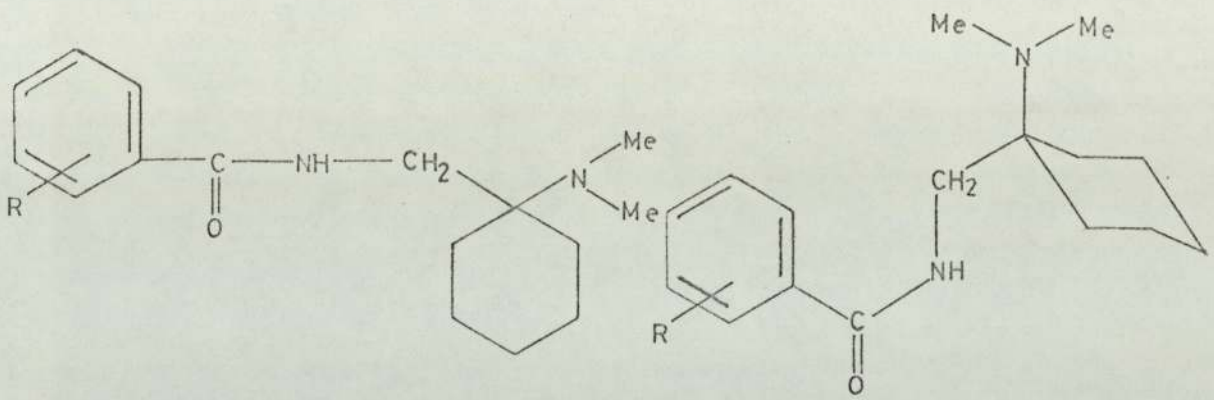
If the analysis of the series is surveyed no conclusions can be drawn as to the relationships between the parameters chosen and the analgetic activity of the compounds. The failure of the Hansch analysis to produce any positive conclusions could be the result of several influencing factors. The two most likely reasons for failure are that the number of compounds analysed was insufficient or that the parameters chosen were not representative of the factors responsible for the analgetic activity of the compounds. The number of compounds included in an analysis should be such that statistical significance can be reached despite errors in measurement. The number of 'degrees of freedom' necessary to obtain significance depends on the accuracy of the measurements and correct parameter values, but as a rough guide four compounds should be included for each parameter. Although this condition is satisfied in the above analysis, the small number of compounds in each analysis will tend to increase the significance of any false value included and thus seriously influence the final result. The other possible reason for the failure is that the parameters chosen were not representative of factors influencing analgetic activity. A great danger in Hansch analysis is too heavy a reliance on intuition for choice of parameters and this can lead to the choice of the wrong parameters or insufficient parameters.

If it is suspected that insufficient parameters have been used this is usually easily remedied. However, in this analysis, neither set of data contained enough compounds to merit the inclusion of another parameter. Thus an explanation of the biological activity in terms of more than one of these parameters (a situation which is most likely when one considers the complexity of analgetic activity) could not be attempted. A further possible reason for failure is that the compounds studied are bringing about their effects by different biological mechanisms, although, in a series of compounds structurally so similar as those studied, this theory can probably be discounted.

In conclusion, it can probably be said that the failure of the analysis to show any good correlation between the parameters examined and analgetic activity is due to a lack of comprehensive data, rather than an incorrect choice of parameters. It is difficult to see that the pKa of the basic group, the electron density of the phenyl ring and the log P values of the compounds do not have any significant influence on their biological activity. Indeed, it is quite possible that, if a sufficient number of active compounds in this series could be obtained to enable the inclusion of all three parameters in a single analysis, some correlation between pKa, electron densities, log P and analgetic activity could be found.

C: Rigid analogues-ring closure approach

Examination of the models of type (49) compounds showed the molecules to be fairly flexible. This flexibility enables each molecule to take up a number of conformations, any one of which may be the preferred conformer most likely to interact with an 'analgetic receptor'. One possible conformation is that the molecule may fold round on itself (82).



(49) (82)

If rigid molecules having a structural similarity to the folded form of the benzamides (82) are synthesised, then the biological activities of these two groups of compounds can be compared. In a situation where the parent compounds (49) and the proposed rigid analogues, the isoquinolones (83), showed similar activities, it becomes feasible that the preferred conformer of the open-chain compounds is one in which the molecule is folded (82). Conversely, if the activities of the compared compounds are dissimilar, it would appear unlikely that the preferred conformation is one in which the molecule is folded as suggested in structure (82). The proposed rigid analogue for initial exploitation is shown in (83) and the synthetic route adopted in Scheme 6.

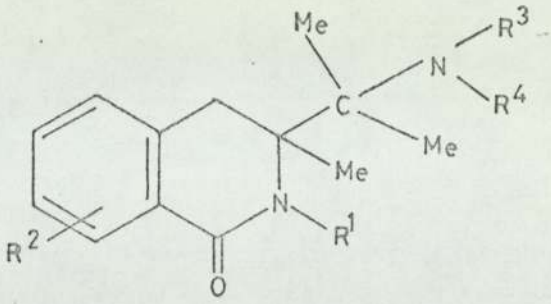
(1). Synthesis of α-aminonitriles and their urethans

The first step in Scheme 6 was carried out using a modification

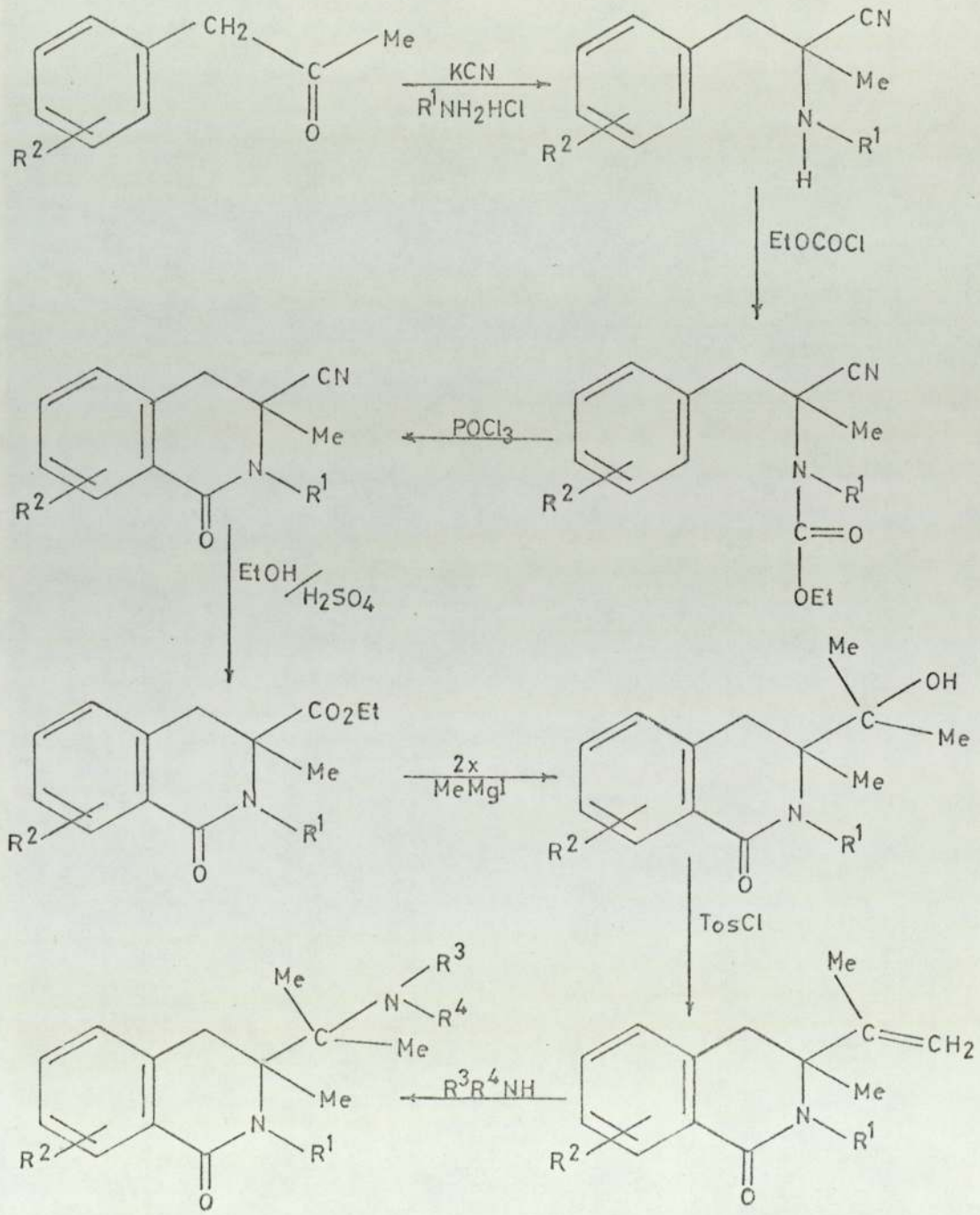
R^1 = alkyl.

R^2 = various.

R^3 = R^4 = alkyl.

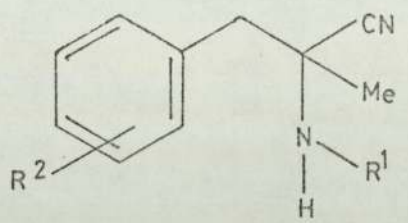


(83)



Scheme 6.

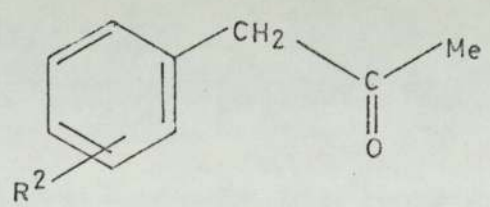
of the Strecker synthesis. α-Aminonitriles of the type (84), substituted on the nitrogen, had not been previously synthesised and so a modification of the method used to synthesise the cyclohexyl α-aminonitrile (47) in Section II A was attempted.



(a) R^2 = H, R^1 = Et.
(b) R^2 = 4-Cl, R^1 = Et.

(84)

The ketones (85) were stirred at room temperature for 3 days with potassium cyanide and ethylamine hydrochloride in the minimum amount of water necessary to effect dissolution.



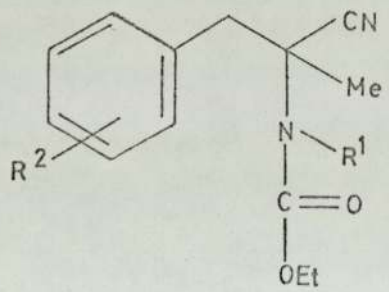
(a) R^2 = H.
(b) R^2 = 4-Cl.

(85)

This method produced the α-aminonitriles in yields rather better (84% for (84a) and 69% for (85b)) than yields obtained by the usual method of refluxing in aqueous ethanol for 6-8 hours (yields of around 60%).

Attempts to make the urethans (86) of these α-aminonitriles by reaction with ethyl chloroformate were unsuccessful. The

mechanism of acylation is thought to be a rate-controlling substitution by the amine on the acyl halide, similar to that for acylation by esters. The failure of these N-substituted α-amino-nitriles to react with ethyl chloroformate is possibly due to steric effects. Although the fact that straight-chain primary amines react faster than ammonia shows the importance of the amine basicity, the reaction is also subject to steric hindrance because secondary amines, although stronger bases than ammonia, react more slowly[80]. Thus, in the case of the α-aminonitriles it is possible that the ethyl substituent on the nitrogen is preventing the reaction from taking place as a result of steric hindrance. If this was the case, the corresponding N-unsubstituted α-aminonitriles should react quite readily with ethyl chloroformate.



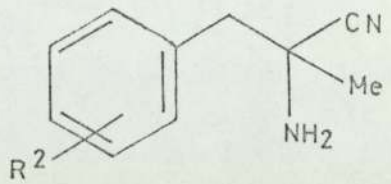
(86)

(a) R^2 = H.

(b) R^2 = 4-Cl.

A number of α-aminonitriles of the type (87) had previously been prepared[81]. The two compounds prepared (87a and b) were synthesised using the method stated above for the N-substituted α-aminonitriles, with ammonium chloride replacing ethylamine hydrochloride. The yields obtained were 95% (87a) and 93% (87b) which, again, in the case of the unsubstituted compound (87a) is an improvement on the value quoted for the usual literature method[81]. Attempts to prepare the urethans of these α-aminonitriles

were slightly more successful.

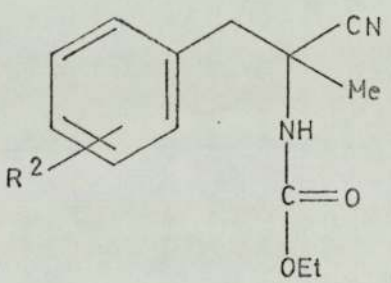


(a) R^2 = H.

(b) R^2 = 4-Cl.

(87)

Reaction of the unsubstituted compound (87a) with ethyl chloroformate in the presence of sodium hydroxide yielded the desired urethan (88).



R^2 = H.

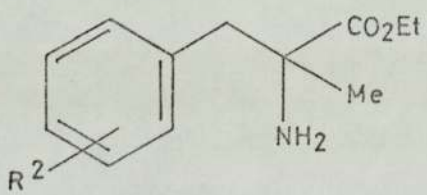
(88)

The 4-chloro-substituted compound (87b), however, failed to react under the same conditions with ethyl chloroformate. Elevation of the temperature of the reaction mixture from 0^o to room temperature also resulted in failure, possibly due to loss of the ethyl chloroformate which is extremely volatile. An increase in the length of reaction time also failed to yield the desired urethan. A possible explanation for this behaviour is that the 4-chloro group on the benzene ring is stabilising the nitrogen lone pair by its electron-withdrawing effect and thus

preventing its reaction with the carbonyl group of ethyl chloroformate.

(2). Synthesis of α-aminoesters and their urethans

During characterisation of the above α-aminonitriles it was discovered that they were thermolabile and it was suspected that under the conditions necessary for ring closure of the urethans the compounds might degrade. Replacement of the cyano group by an ester group would not only render the molecules potentially more stable but also eliminate the necessity of the hydrolysis step from CN to COOEt in Scheme 6. Two compounds of the type (89) were prepared using literature methods[82,83,81].

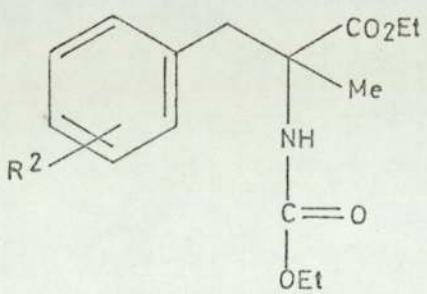


(a) R^2 = H.

(b) R^2 = 3,4-diMeO.

(89)

Reaction of the two compounds (89a and b) with ethyl chloroformate in the presence of sodium hydroxide was successful in both cases, yielding the respective urethans (90).



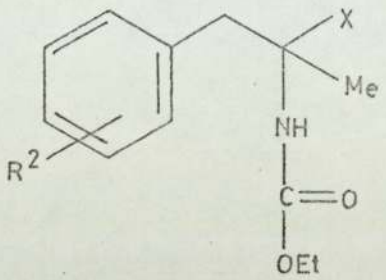
(a) R^2 = H.

(b) R^2 = 3,4-diMeO.

(90)

(3). Ring closure of urethans

The ring closure of the urethans (91) is a modification of the Pictet-Spengler reaction for the synthesis of tetrahydroisoquinolines.

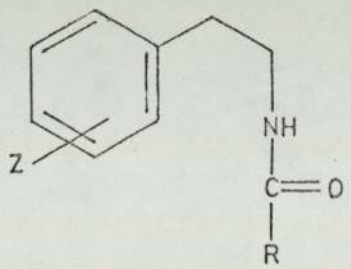


(91)

R^2 = H or 3,4-diMeO.

X = CN or COOEt.

The Pictet-Spengler reaction is essentially a form of the Bischler-Napieralski reaction and it is known[84] that isoquinoline derivatives having a hydroxyl function in the 1-position may be obtained by replacing the usual starting amide (92) with a urethan.



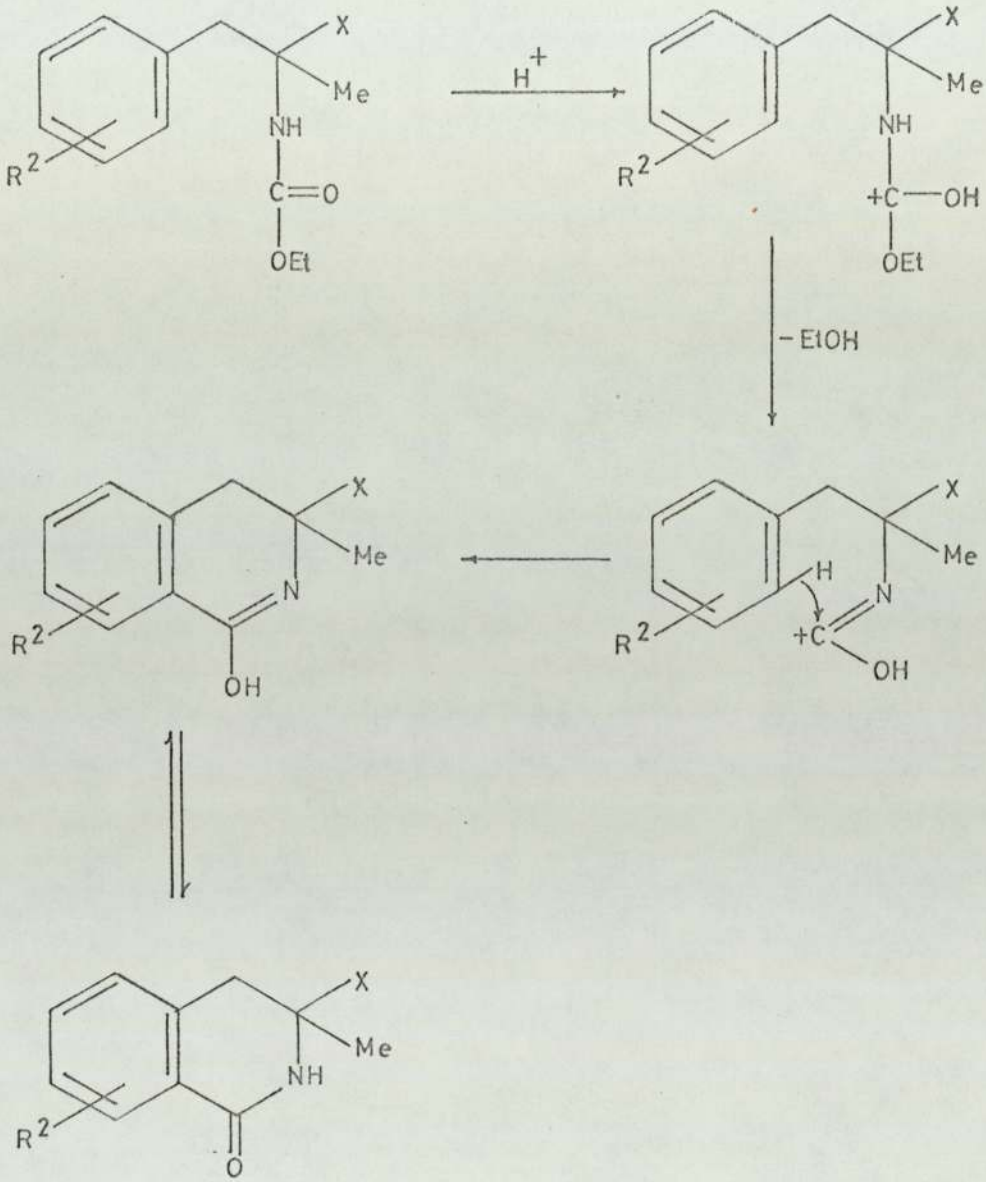
(92)

Z = various substituents.

R = alkyl or aryl.

Although no direct mechanistic study has been carried out on the Pictet-Spengler reaction, it seems likely to take the same course as other aromatic substitutions by electrophilic attack (Scheme 7). The reactivity of the aromatic nucleus is important to the success of the reaction. The reaction is facilitated by having an increased electron density at the point of proposed ring closure. This

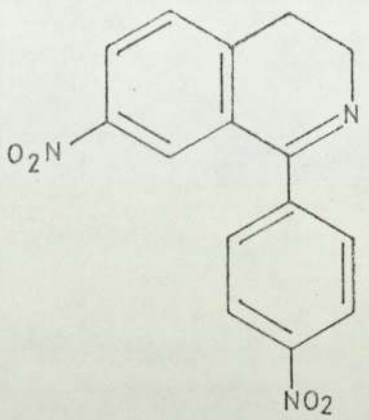
condition is satisfied if the aromatic ring is substituted with an electron-donating group (for example, alkoxy, hydroxy) at a position para to the point of ring closure.



Scheme 7.

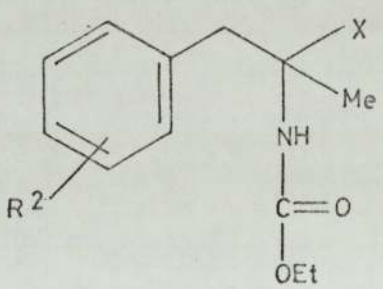
Indeed, few isoquinolones have been synthesised without the presence of this electron-donating moiety. No compounds containing electron-

withdrawing groups in the aromatic nucleus have been synthesised, with the exception of the 3,4-dihydroisoquinoline (93) which was prepared using the Bischler-Napieralski method[85].



(93)

The three compounds with which cyclisation was attempted were (91a, b and c).



(91)

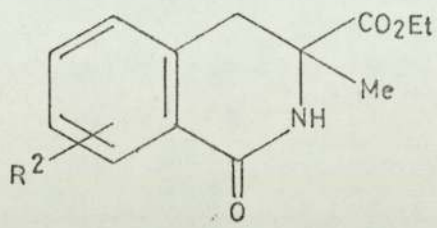
(a) R^2 = H, X = CN.

(b) R^2 = H, X = COOEt.

(c) R^2 = 3,4-diMeO, X = COOEt.

Attempts to cyclise (91a and b) were unsuccessful using phosphorus oxychloride in refluxing chloroform for 4 hours. It was thought that an increase in the temperature at which cyclisation was attempted might yield the desired product, but refluxing in phosphorus oxychloride at 105° for 4 hours yielded only starting materials in almost quantitative yield. Replacement of the phosphorus oxychloride by a more powerful cyclising agent, polyphosphoric ester, did not yield the desired product. An attempt to cyclise

(91c) by refluxing in chloroform with phosphorus oxychloride for 2 hours was also unsuccessful, but refluxing in phosphorus oxychloride at 105° for 2 hours yielded the desired cyclised product (94).

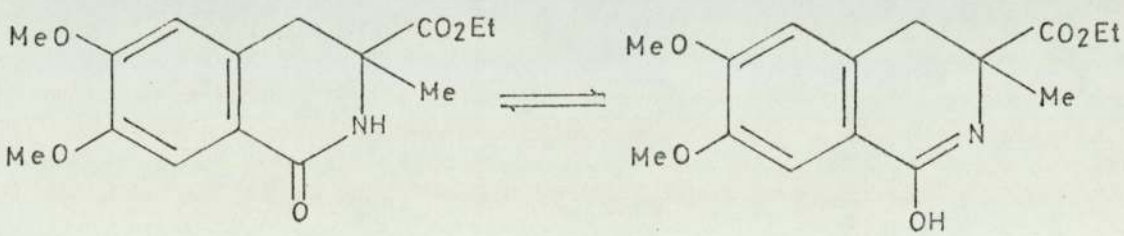


R^2 = 6,7-diMeO.

(94)

The cyclised compound was one in which an electron-donating group was present in a position para to the point of cyclisation. Although a few compounds unsubstituted in the aromatic ring have previously been cyclised[86], the present attempts on unsubstituted compounds both failed, giving an indication of the importance of the activation of the aromatic nucleus in this cyclisation reaction.

The isoquinolone (94) can exist in two forms- the enol form (95) and the keto form (94), an equilibrium being possible between the two forms.



(94) (95)

In the case of 1-hydroxyisoquinoline it has been shown[87] by a

U/V spectometric method that the ratio of the equilibrium is 18,000:1 in favour of the amide form. This study was carried out in neutral aqueous solution at 20° and, although the method cannot detect isomers in a concentration of less than 1%, it confirms that the amide is the favoured form. Further work on this enol-amide equilibrium included an infrared study of α- and γ-hydroxy N-heterocyclic compounds[88]. 1-Hydroxyisoquinoline was found to absorb in the amide (1630-1780cm^{-1}) and NH (3360-3500cm^{-1}) regions, thus confirming the predominance of the amide form. In the solid state 1-hydroxyisoquinoline has strong absorptions at 3150cm^{-1} and 1653cm^{-1}. This compares favourably with the absorptions of 3120cm^{-1} and 1680cm^{-1} observed for compound (94). Thus, it is reasonable to assume that compound (94) exists mainly in the amide form.

An attempt at the subsequent stage in Scheme 6, that is, reaction of compound (94) with 2 moles of methyl magnesium iodide, proved unsuccessful and, as a result, Scheme 6 was not completed.

The one isoquinolone obtained by the ring closure route was submitted to a primary pharmacological screen and was found to be analgetically inactive (although a small degree of activity was recorded in the hot-plate test). This result is not too surprising as the molecule does not contain a basic centre, a feature apparently necessary for analgetic activity.

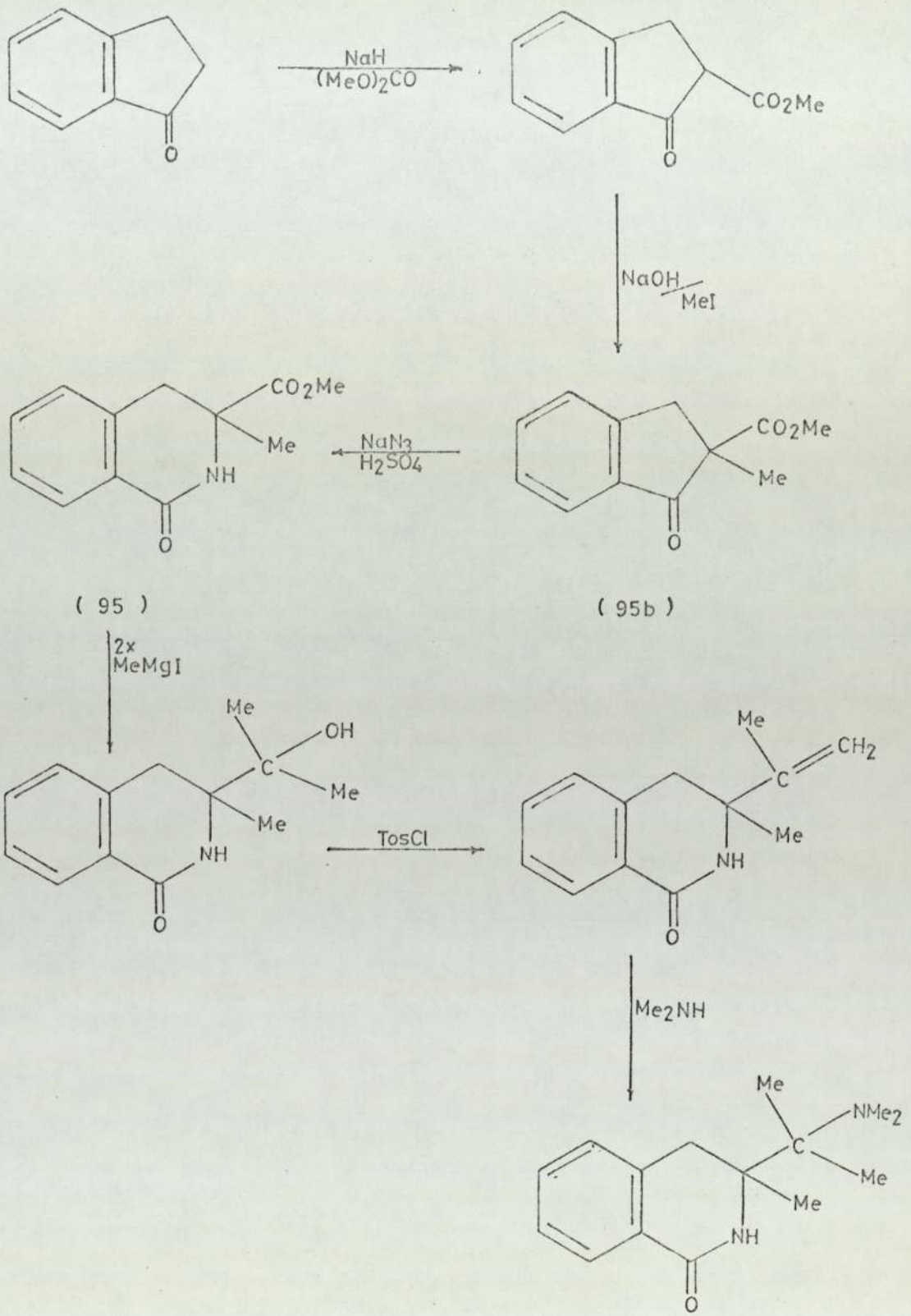
D: Rigid analogues-ring expansion approach

As a result of a survey of the literature and practical experience with the compounds in the previous Section, it became apparent that the original synthetic route to the model compound (83) was impracticable. Thus it was decided to investigate another method for the synthesis of isoquinolones. A method considered to be suitable was the ring expansion of 1-indanones to 1(2H)-isoquinolones using hydrazoic acid-the Schmidt reaction.

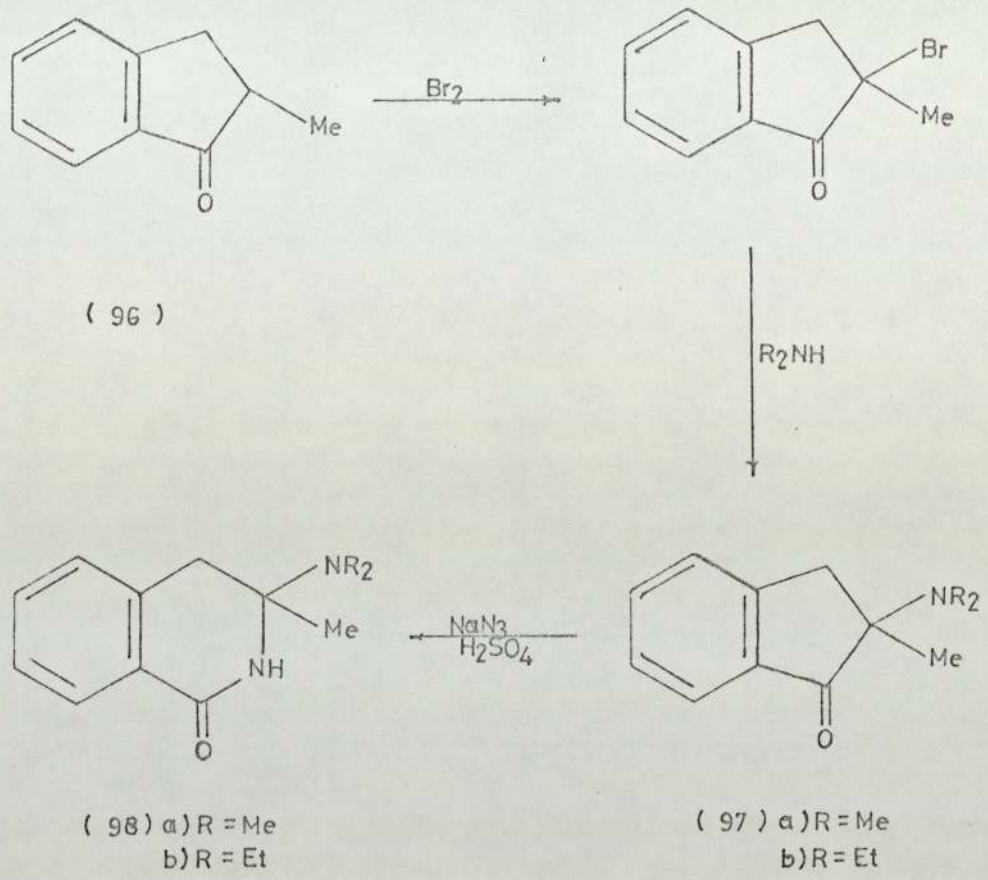
The original intention in this area of work was to synthesise a compound structurally analogous with the isoquinolone produced by the ring closure method. The compound finally chosen (95) and its method of synthesis are shown in Scheme 8. Although the compound (95) is not strictly analogous in that the benzene ring is unsubstituted and the ester is a methyl, not an ethyl, ester, the overall structure of the molecule is basically similar. Scheme 8 was partially successful and compound (95) was synthesised. An attempt at the subsequent step in the synthetic pathway (Scheme 8), that is, attack on the ester group by 2 moles of methyl magnesium iodide, produced only an almost quantitative return of starting material. Obviously other methods for the introduction of a basic group into these molecules had to be found.

(1). Substitution versus elimination

As a result of the failure to introduce a basic group into the isoquinolones so far produced another synthetic scheme was investigated (Scheme 9). In this synthetic scheme (9) the basic group has been introduced directly onto the ring instead of being separated from it by one carbon, as proposed in Scheme 6. The preparation of two compounds (98a and b) were attempted by Scheme 9. Compound (97a) had previously been prepared by Büchi and co-


NaH
(MeO)2CO
CO2Me
NaOH
MeI
CO2Me
Me
NH
O
NaN3
H2SO4
CO2Me
Me
O
(95)
(95b)
2x
MeMgI
Me
OH
C
Me
Me
NH
O
TosCl
Me
CH2
C
Me
NH
O
Me2NH
Me
NMe2
C
Me
Me
NH
O

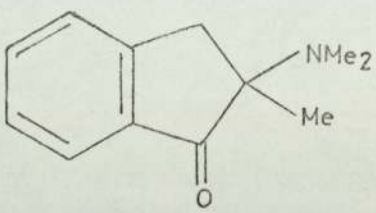
Scheme 8.



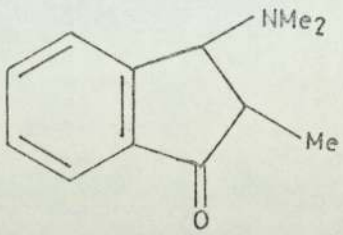
Scheme 9.

workers[89] and this method was applied to the synthesis of both compounds (97a and b). Büchi reported that by reaction of dimethylamine with 2-bromo-2-methyl-1-indanone two compounds were obtained. The report indicated that the 2,2-disubstituted compound (97a) was isolated in good yield (70%), followed by the 2,3-disubstituted compound (99) in poor yield (25.3%). However, in the present study, the reaction of dimethylamine and diethylamine with the 2-bromo compound yielded only the 2,3 isomer in both cases in yields of 26.3 and 7.5% respectively. In correspondence, Büchi confirmed[90] that the total yield of the two isomers was only 13.5% and the possibility that, in the present study, the 2,2 isomer was being formed in amounts too small to be detected could be postulated.

This, however, still does not agree with the previously published work[89] which stated that the major proportion of the mixture consisted of the 2,2 isomer and that this was isolated first.



(97a)



(99)

That the compound obtained in the case of reaction with dimethylamine was the 2,3 isomer was shown by comparison of the physical characteristics of the compound obtained with those previously quoted (Table 6).

DATA	COMPOUND (100)	(99) 2,3 ISOMER	(97a) 2,2 ISOMER
IR C=O	1715 cm^{-1}	1720 cm^{-1}	1695 cm^{-1}
m.p.	162.5°	162°	218°
NMR	τ 8.55 d 3H τ 6.40 m 1H τ 5.10 d 1H	τ 8.45 d 3H τ 6.90 m 1H τ 4.98 d 1H	τ 8.40 s 3H τ 7.10 s 6H τ 6.45 q 2H

Table 6

Similarly, by comparison of the physical characteristics of the compound obtained by reaction with diethylamine, it was shown that compound (97b) was probably also the 2,3 isomer (Table 7). In a consideration of the NMR data of Table 7, account must be taken of the replacement of the dimethylamino portion of the original molecule (97a) by diethylamino. The signal at τ 8.55 shows an

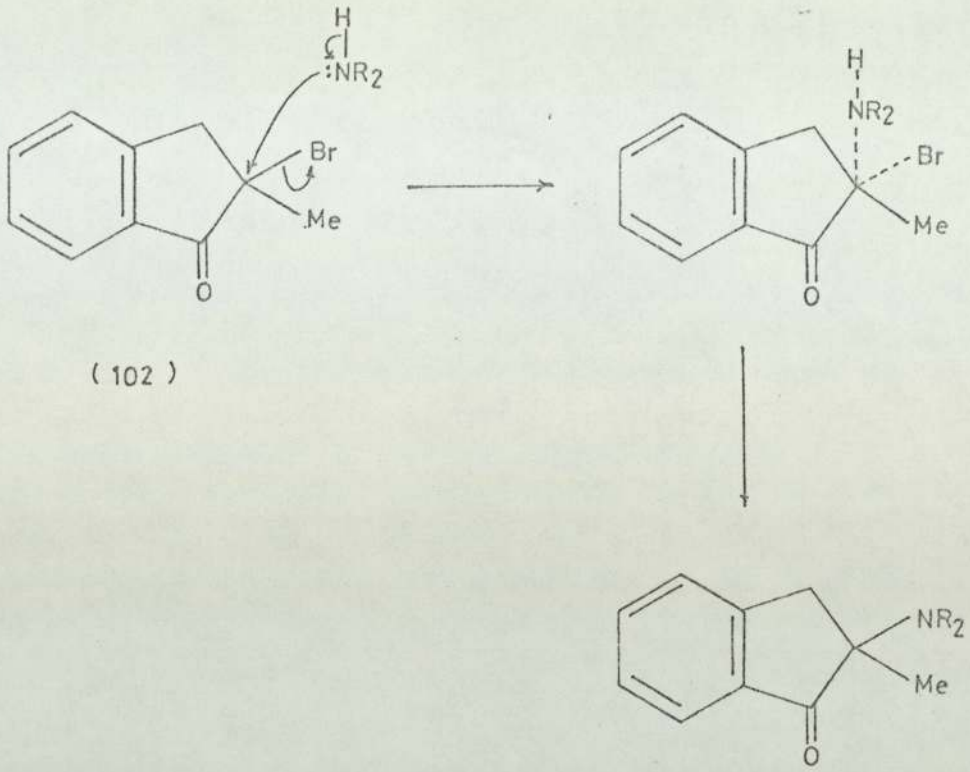
integral for nine protons in the form of a multiplet.

DATA	COMPOUND (101)	2,3 ISOMER (99)
IR C O	1720 cm^{-1}	1720 cm^{-1}
m.p.	142°	162°
NMR	8.55 m 9H 6.80 m 5H 5.05 d 1H	8.45 d 3H 6.90 m 1H 4.98 d 1H

Table 7

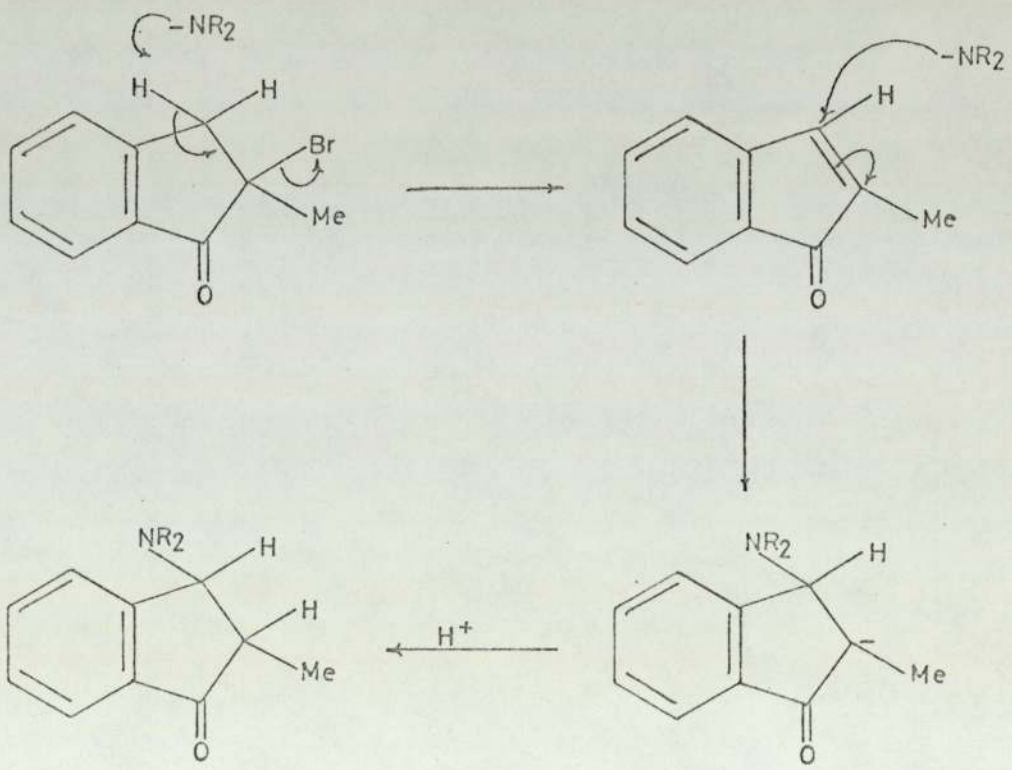
This is due to the coincidence of the signal for the methyl portions of the diethylamino group (normally a triplet integrating for six protons) and the signal for the protons of the 2-methyl group (normally a doublet). Similarly, the signal at τ 6.80 is a multiplet which has an integral value for five protons, comprising of the four proton quartet of the diethylamino group together with the one proton multiplet of the proton on C-3. The proton on C-2 is unaffected directly by any change in the amine group and thus the one proton doublet is in its usual position at about τ 5.00.

The reason for the formation of these two isomers is probably the result of two competing reaction mechanisms for the reaction of the amine with 2-bromo-2-methyl-1-indanone. That the E2 elimination mechanism is analogous to and competes with S_N2 substitution is known[92]. The two isomers obtained by the reaction of the amines with 2-bromo-2-methyl-1-indanone were suspected to result from these competing mechanisms. S_N2 substitution of compound (102) by an amine would lead to the 2,2-disubstituted isomer (Scheme 10). An E2 elimination would give rise to the 2,3-disubstituted isomer by elimination followed by an addition across the double bond (Scheme 11).



(102)

Scheme 10.



Scheme 11.

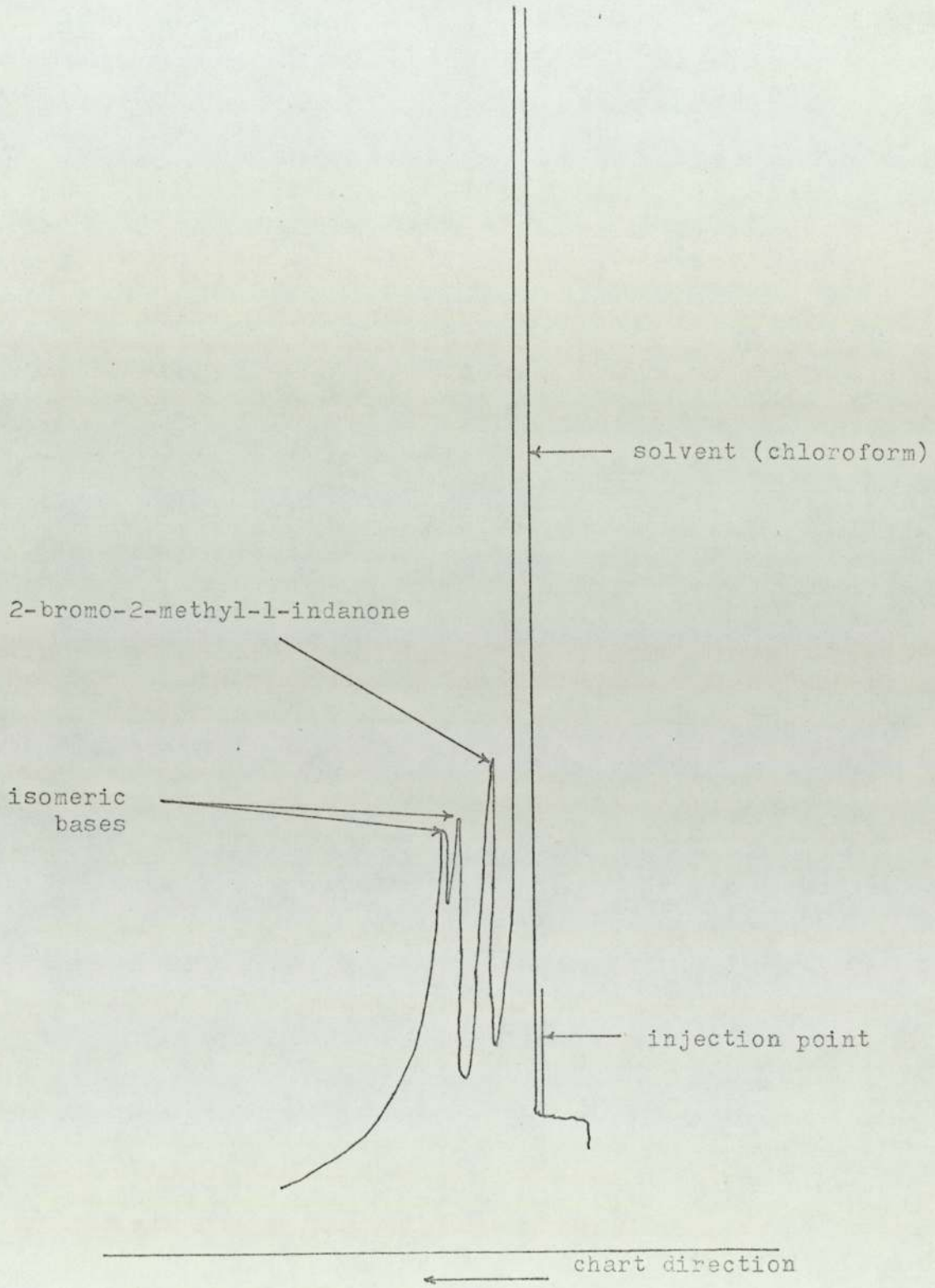

solvent (chloroform)
2-bromo-2-methyl-1-indanone
isomeric
bases
injection point
chart direction

Figure 1.

Consequently, it was decided to investigate the mechanistic course of the reaction by variation of the reaction conditions and examining the way in which the ratio of the products obtained varied with the conditions used. If the conditions were chosen so that either elimination or substitution should be the preferred reaction, then an examination of the ratio of the compounds produced should give an indication of whether the situation was one of substitution versus elimination. Initially, however, it was necessary to prove that both compounds were formed, because, in this present study, the 2,2 isomer had never been isolated. An examination was made of the mixture obtained from the reaction of diethylamine with 2-bromo-2-methyl-1-indanone. The reaction was carried out at room temperature for 24 hours in absolute ethanol, using a 2.5x excess of diethylamine. Diethylamine was used in preference to dimethylamine because of its higher boiling point and is, practically, more easily handled.

A gas-liquid chromatographic examination of a chloroform solution of the mixture of bases obtained was carried out using an OV 17 (5%) column. Injection of 1μlitre of the solution (0.92%) with an oven temperature of 170^{o} and an amplification of 20 yielded the spectrum in Figure 1. From Figure 1 it can be seen that there are, indeed, two components in the mixture. Assuming these two components to be the two bases, a study of how variation in reaction conditions affected the ratio of the isomers produced was carried out. The method used for the determination of the ratio of the two isomers was one involving a solution infrared study (for details see Experimental Section). The results obtained can be seen in Table 8.

From an examination of Table 8 the effect of various changes

COMPOUND	CONDITIONS				RATIO
	SOLVENT	TEMP.	TIME	BASE	2,2:2,3 ISOMER
(103a)	EtOH	27°	24hr	5x diethylamine	1:1.203
(103b)	EtOH	27°	24hr	2½x diethylamine	1:1.09
(103c)	EtOH	27°	24hr	10x diethylamine	1:1.41
(103d)	EtOH	27°	24hr	5x dipropylamine	1:1.388
(103e)	EtOH	27°	24hr	5x dibutylamine	1:1.433
(103f)	EtOH	27°	24hr	5x diphenylamine	no 2,2 cpd.
(103g)	50% EtOH	27°	24hr	5x diethylamine	1:1.382
(103h)	75% EtOH	27°	24hr	5x diethylamine	1:1.64
(103i)	EtOH	80°	24hr	5x diethylamine	no 2,2 cpd.

Table 8

in reaction conditions on S_N2 substitution versus E2 elimination can be seen. The first effect which can be examined is the effect of the substrate structure. Under second-order conditions α-branching increases elimination, to the point where tertiary substrates undergo few S_N2 reactions and two reasons could be presented to explain this trend. One is that, as α-branching increases, there are usually more hydrogens available for the base to attack. The second reason is that α-branching increases steric hindrance to the attack of the base at the carbon. If the ratios of isomers obtained from the four bases used (diethylamine, di-n-propylamine, di-n-butylamine and diphenylamine) are examined, it can be seen that, as the size of the base increases, the ratio of the elimination/addition product increases to a point where, in the case of diphenylamine, no 2,2 isomer is produced. Although this steric effect of the attacking base is not strictly analogous to the steric effect of the substrate previously mentioned, it can be seen that, as the size of the base increases, substitution will become more difficult, leading to an increase in the production of

the 2,3 isomer.

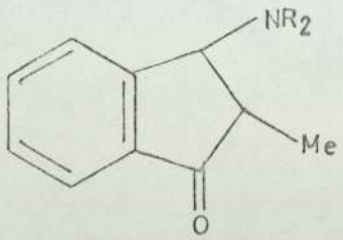
The second effect to be examined was that of the solvent. As the solvent polarity is increased the S_N2 reactions are favoured at the expense of E2 reactions. From an examination of Table 8, it can be seen that increasing the polarity of the solvent by using 50% and 75% aqueous ethanol instead of absolute ethanol had the effect of increasing the amount of 2,3 isomer. This is not the expected result if the reaction is one in which elimination competes with substitution. However, an additional factor may be involved here as 2-bromo-2-methyl-1-indanone is insoluble in water and the use of aqueous ethanol tends to lead to reaction of a suspension of 2-bromo-2-methyl-1-indanone with diethylamine. Thus a solubility factor may be having an effect on the ratio of the two isomers produced.

As the temperature of the reaction is increased elimination is favoured at the expense of substitution and this can be seen to be the case in the present study. Increasing the temperature from room temperature to a temperature sufficient to reflux (about 80°) the reaction mixture leads totally to an elimination/addition product.

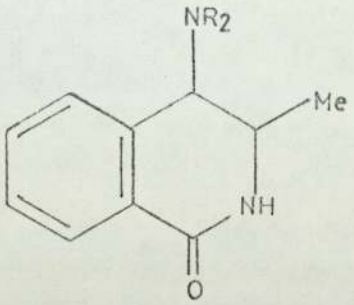
The final effect examined was that of the concentration of the base used. High concentrations of base favour elimination whereas lower concentrations favour substitution. This is apparently the case in this study, as increasing the concentration of diethylamine used from 2.5x $\longrightarrow$ 5x $\longrightarrow$ 10x excess gave a steady increase in the proportion of 2,3 isomer produced. An equimolar quantity of diethylamine was attempted but the total yield of isomers produced was insufficient to allow a determination of the ratio of the products. From all the above results it appears likely that, although there is no totally conclusive evidence, the situation is,

indeed, one of E2 elimination versus S_N2 substitution.

The two 2,3 isomers isolated (99 and 101) were both ring-expanded to 3,4-disubstituted isoquinolones, using the Schmidt reaction.

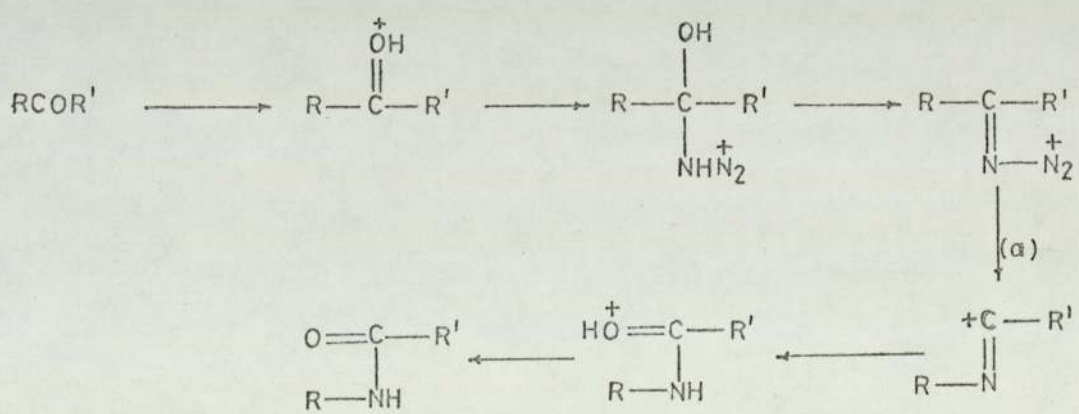


(99) R = Me
(101) R = Et



(104) a) R = Et
b) R = Me

The Schmidt reaction, in fact, covers a number of related reactions of hydrazoic acid with various types of organic molecules in the presence of strong acid. The most important Schmidt reactions are those carried out with carbonyl compounds and the currently accepted mechanism, proposed by Oliveri-Mandala[91], is set out in Scheme 12.



Scheme 12.

The crucial step is the rearrangement, step (a), and in the case of ketones there are two possible migrating groups leading to two possible products, isoquinolones and quinolones. A discussion

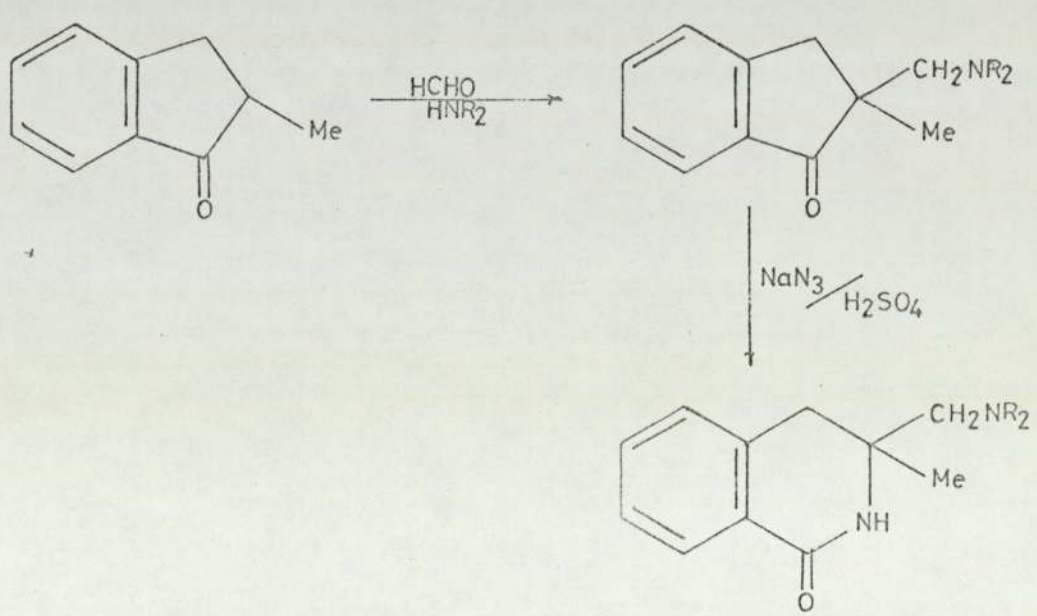
regarding the nature of the products formed by ring expansion during this study can be found later in this section.

The reaction was carried out on compounds (99 and 101) using sodium azide in a medium of concentrated sulphuric acid and yielded the two compounds (104a and b).

Compound (101) was subjected to CNS pharmacological testing and was found to have no analgetic activity. No pharmacological results are available, as yet, for the two isoquinolones (104a and b).

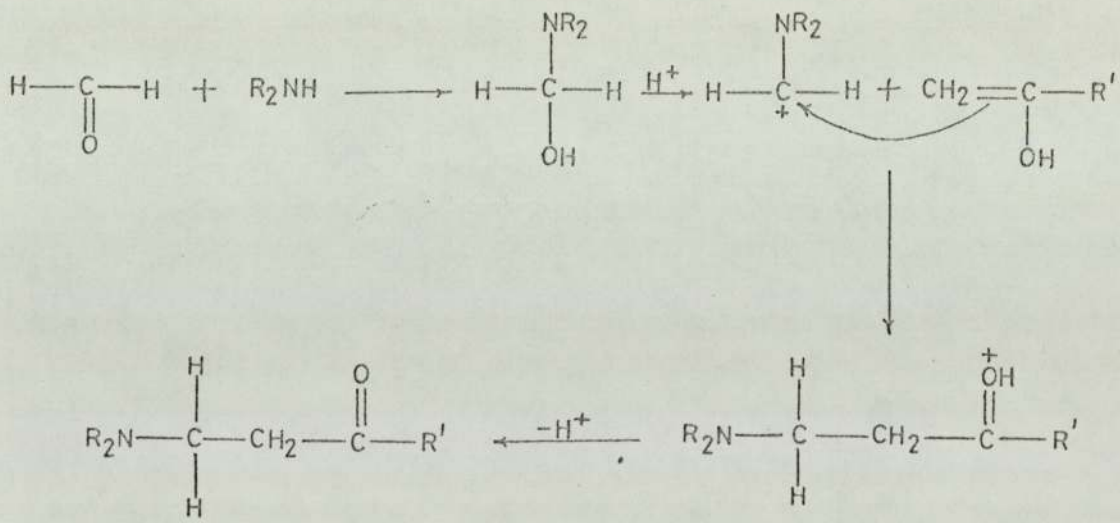
(2). Preparation and properties of some 2-substituted-1-indanones

Although compound (101) showed no analgetic activity, it must be borne in mind that the basic group is attached directly to the ring, whereas in the model compound (83) the basic group is separated from the ring by a carbon atom. In order to introduce this carbon atom a new synthetic route had to be considered. If 2-methyl-1-indanone undergoes a Mannich reaction and the Mannich base so produced is ring-expanded, then the introduction of this carbon atom would be achieved (Scheme 13).



Scheme 13.

The Mannich reaction consists of the condensation of ammonia, or a primary or secondary amine, with formaldehyde and a compound containing a reactive hydrogen. The mechanism of the Mannich reaction has been a source of controversy with respect to whether formaldehyde is first attacked by the active hydrogen compound or by the amine. The evidence now seems to favour the latter mechanism[92]. In the acid-catalysed reaction it is thought that the reaction proceeds by the mechanism outlined in Scheme 14.

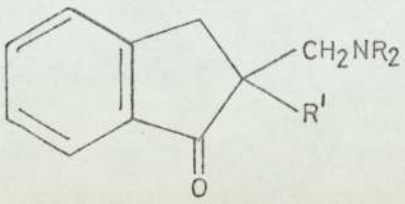


Scheme 14.

In this mechanism, it is the free amine and not the amine salt which reacts, even in acid solution; the active hydrogen compound reacts as the enol when that is possible.

The Mannich reaction has previously been attempted using 1-indanones. 1-Indanone itself has been treated with morpholine hydrochloride and formaldehyde to yield 2-morpholinomethyl-1-indanone in 83% yield[93]. More recently[94,95], several Mannich bases of the type (105a) have been prepared. However, no Mannich bases of 2-methyl-1-indanone have previously been prepared and it was

decided that several compounds of the type (105b) should be prepared, using various amines.



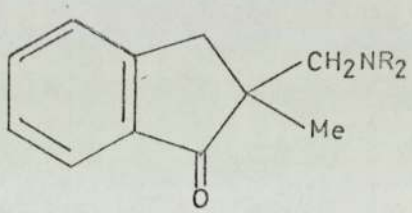
(a) R' = H.

(b) R' = Me.

(105)

The general method used was to reflux 2-methyl-1-indanone, the amine or its hydrochloride salt, 40% formalin solution or paraformaldehyde and concentrated hydrochloric acid for various periods of time. After working up, this method yielded the Mannich bases in yields shown in Table 9.

BASE (NR_2)	YIELD %
Dimethylamino	83.5
Diethylamino	18.9
Piperidino	17.8
Morpholino	19.5
$\underline{N}^4$-methylpiperazino	62.8



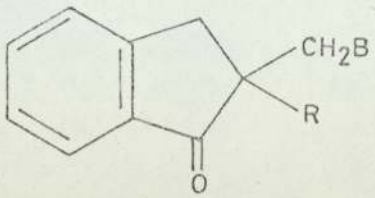
(105 b)

Table 9

Also prepared were the corresponding Mannich bases of the type (105a), several of which had been previously prepared.

The two series of indanones, (105a and b), were submitted to a primary pharmacological screen. The qualitative results of the primary screen are shown in Table 10 (for more detailed results see Tables 18,19,20 in Pharmacology section). As can be seen from Table 10 not enough pharmacological results have been received to

enable any structure-activity relationships to be formulated in these two series of compounds.



(106) R = H.

(107) R = Me.

(a) B = dimethylamino.
(b) B = diethylamino.
(c) B = piperidino.
(d) B = morpholino.
(e) B = $\underline{N}^4$-methylpiperazino.

COMPOUND	HOT-PLATE TEST	PHENYLQUINONE TEST
(106a)	No results available	No results available
(106b)	No results available	No results available
(106c)	Toxic	Toxic
(106d)	No results available	No results available
(106e)	No results available	No results available
(107a)	No results available	No results available
(107b)	Inactive	Negligible activity
(107c)	No results available	No results available
(107d)	No results available	No results available
(107e)	Marked activity	Marked activity

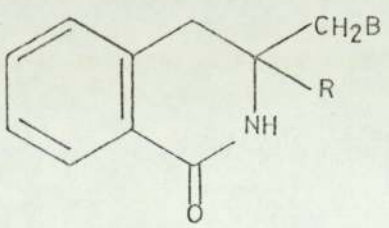
Table 10

However, the compounds for which results have been received show a remarkable degree of variation in their activities. Compound (106c) was very toxic and caused the death of almost all the test animals used. Compound (107b) was found to have no activity in the hot-plate test, showing no significant increase in reaction time compared to an injection of saline. In the phenylquinone test, however, compound (107b) showed a small amount of activity, causing 30.7% inhibition of writhing at a dose of 400μM/Kg percutaneously,

compared with 45% inhibition caused by a dose of 40μM/Kg of codeine. No toxicity was found using this compound. Compound (107e) showed marked activity in the hot-plate and phenylquinone tests. In the hot-plate test injection of 50mg/Kg subcutaneously of compound (107e) caused a marked increase in reaction time. Further investigations in this test yielded an ED_{50} value of 27mg/Kg (18.8-52.6) compared with an ED_{50} value of 14mg/Kg (7.3-26.6) for codeine. Administration of 100mg/Kg of compound (107e) caused convulsions from which all the mice recovered. Because of these convulsions, which are an indication of narcotic-like activity, no further interest was shown in the compound. In the phenylquinone test 100mg/Kg percutaneously of compound (107e) caused 98.5% inhibition of writhing, compared with 76.8% inhibition caused by 10mg/Kg of codeine. ED_{50} evaluation of the compound is being carried out in the phenylquinone test.

(3). Preparation and properties of some 3-substituted-1-oxo-isoquinolines

All the compounds in the two series of indanones, (105a and b), were ring-expanded to isoquinolones using hydrazoic acid in a manner analogous to that for the 2,3-disubstituted indanones (99 and 101). The yields of the compounds obtained can be found in Table 11.



(108) R = H.

(109) R = Me.

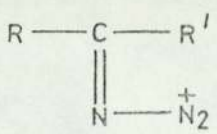
(a) B = dimethylamino.
(b) B = diethylamino.
(c) B = piperidino.
(d) B = morpholino.
(e) B = N^4-methylpiperazino.

COMPOUND	YIELD %
(109a)	87.9
(109b)	2.2
(109c)	18.1
(109d)	59.6
(109e)	7.9
(108a)	27.3
(108b)	65.5
(108c)	86.4
(108d)	81.6
(108e)	81.3

Table 11

Certain of the compounds in the series without the 2-methyl substituent (108) had previously been reported in a patent[94]. The patent stated that only one compound was obtained in all cases, although it is known from previous work[96] that mixtures of isomeric amides are usually formed in reactions of this type. In all the Schmidt reactions carried out as stated above only one product was obtained. A decision was taken to show that, although the crucial rearrangement step of the Schmidt reaction allows the production of two isomers, only one isomer is, in fact, being produced in this present study.

Investigation into this isomerism was first carried out by Smith and Horowitz[96], who examined certain substituted benzophenones and arylalkyl ketones. They considered that the intermediate (110), which is a feature of the mechanism of the Schmidt reaction, has a structure which indicates the possibility of geometrical isomerism.

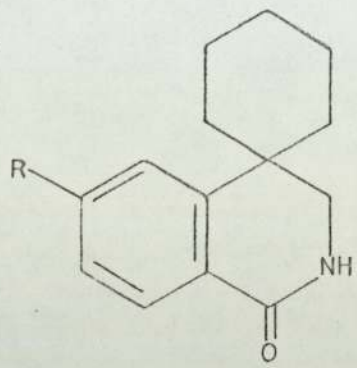


(110)

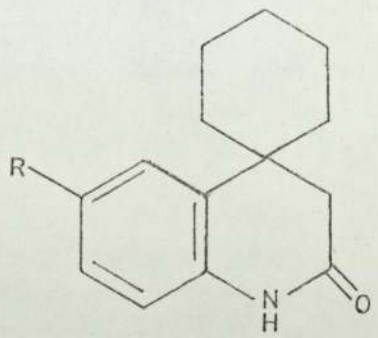
The suggestion was made that if the trans group migrates from C to N as in the Beckmann rearrangement, the ratios of the syn and anti configurations would determine the relative extents of migration of R and R'. An investigation was then made to demonstrate whether the 'migration aptitudes' (that is, relative rates of migration) of the migrating groups determined the ratio of the isomeric amides produced in the Schmidt reaction. The work was carried out using a series of para-substituted benzophenones and it was found that the ratio of amides produced was almost independent of the para substituents. However, an examination of the steric factors involved in the rearrangement showed that great changes in the ratios of amides could be brought about by an alteration of the steric environment of the carbonyl group. A series of arylalkyl ketones of the type Ph-CO-R (R = methyl, ethyl, isopropyl, tert-butyl) was examined and it was found, from the migration ratios, that as the alkyl group became more branched (that is, steric effects increased) then the preferred migration changed from phenyl to alkyl migration. It is also worth noting that this same branching had a retarding effect on the reaction as a whole, giving poorer overall yields as the branching was increased. More recently[97] it has been shown that 1-indanones containing no substituents in the benzene ring yielded quinolones as the sole isolable product. This information, when compared with the reported products in the patent[94], appears to be contradictory. On the basis of this apparent contradiction it was decided to investigate the ring expansion of the two series of indanones (105a and b) to a greater extent.

Initially it was necessary to prove whether the sole isolable product obtained was an isoquinolone or a quinolone. A method of comparison by examination of the infrared frequency of the carbonyl

groups had previously been attempted[97] and a small difference ($\sim 5cm^{-1}$) had been observed, the isoquinolone (111) having lower frequencies than the quinolone (112).



(111)



(112)

$R = OCH_3$	C=O freq. = $1660cm^{-1}$	$R = OCH_3$	C=O freq. = $1665cm^{-1}$
R = H	C=O freq. = $1670cm^{-1}$	R = H	C=O freq. = $1675cm^{-1}$

However, this difference is too small to assign a structure to a compound with any degree of certainty. In the same study[97] a U/V method of identification was used. This method consisted of reduction of the quinolones and isoquinolones to their respective bases and examination of the effect of the addition of acid on the U/V spectra. The results showed that the compounds derived from isoquinolones had unchanged spectra, whereas those derived from quinolones exhibited a hypsochromic shift, indicating that the nitrogen was attached to the benzene ring. The possibility existed that the U/V spectra of the isoquinolones and quinolones themselves were sufficiently different to allow identification and this was investigated.

The U/V spectra of the two series of ring-expanded compounds produced were run and compared with the spectra of quinolone (113) and the isoquinolone (114) which had been prepared by unambiguous routes. These two reference spectra can be seen in Figures 2 and 3 respectively. The assumption was made that substituents in the 3

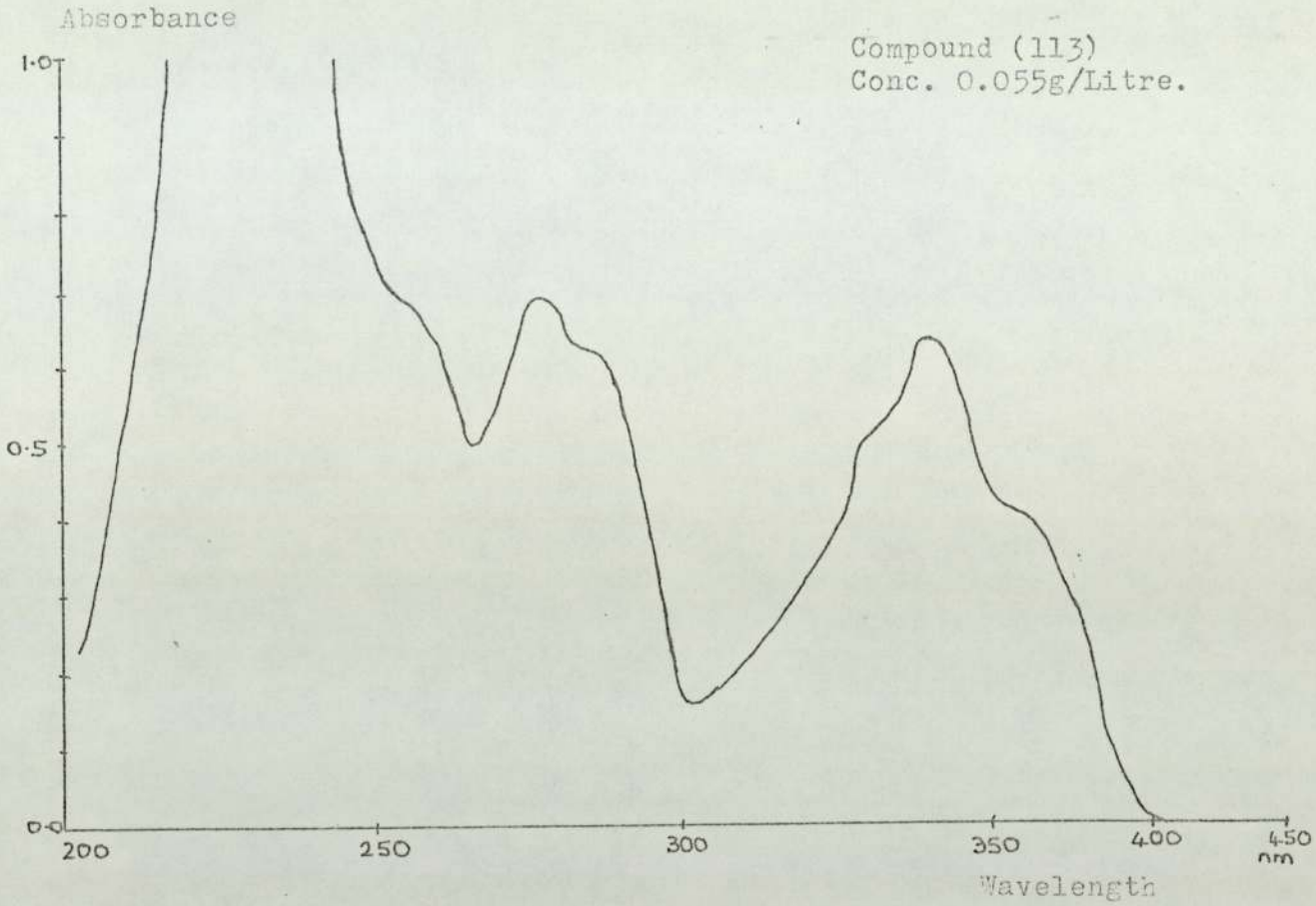


Figure 2.

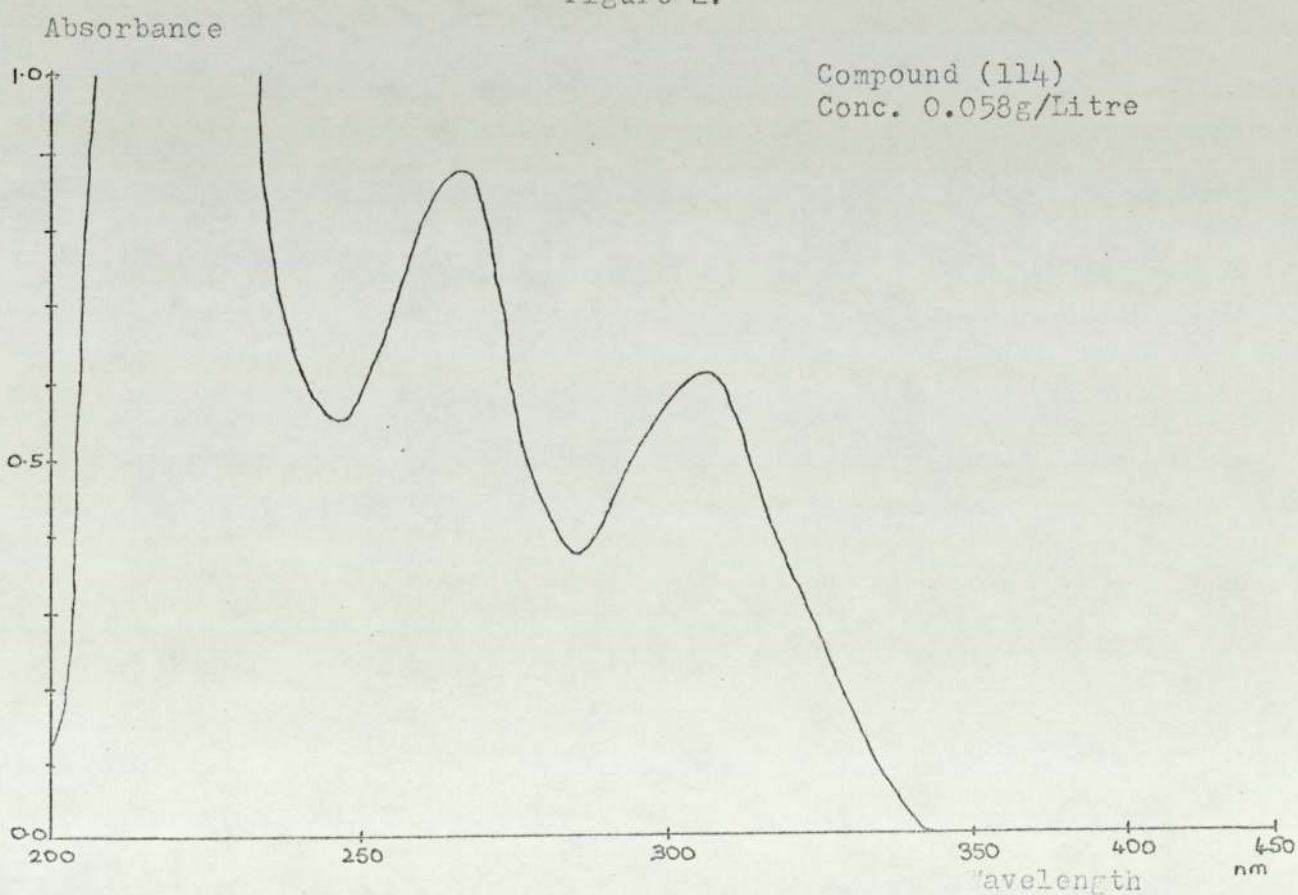
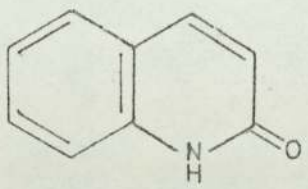
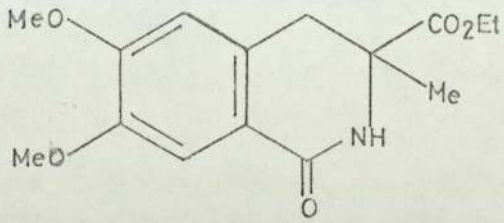


Figure 3.

position of the compounds under examination would not significantly alter the U/V spectra and thus each U/V spectrum obtained was compared with the two standard spectra.



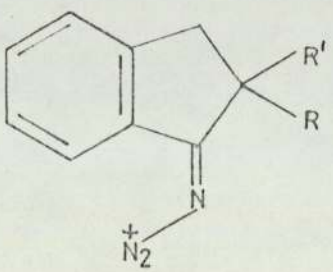
(113)



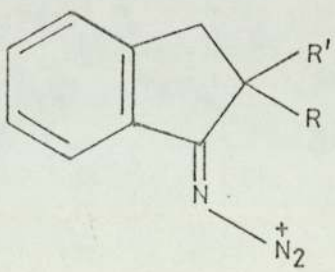
(114)

The results obtained can be seen in Table 12. By comparison of the spectra obtained with those of the two reference compounds it can be seen that all the compounds have spectra similar to the iso-quinolone (114), except compound (116) which had a spectrum similar to that of quinolone (113).

If it is assumed that the intermediate (115) can exist in the cis (a) and trans (b) (to the benzene ring) forms, then an equilibrium situation can exist (Scheme 15).



(115a)



(115b)

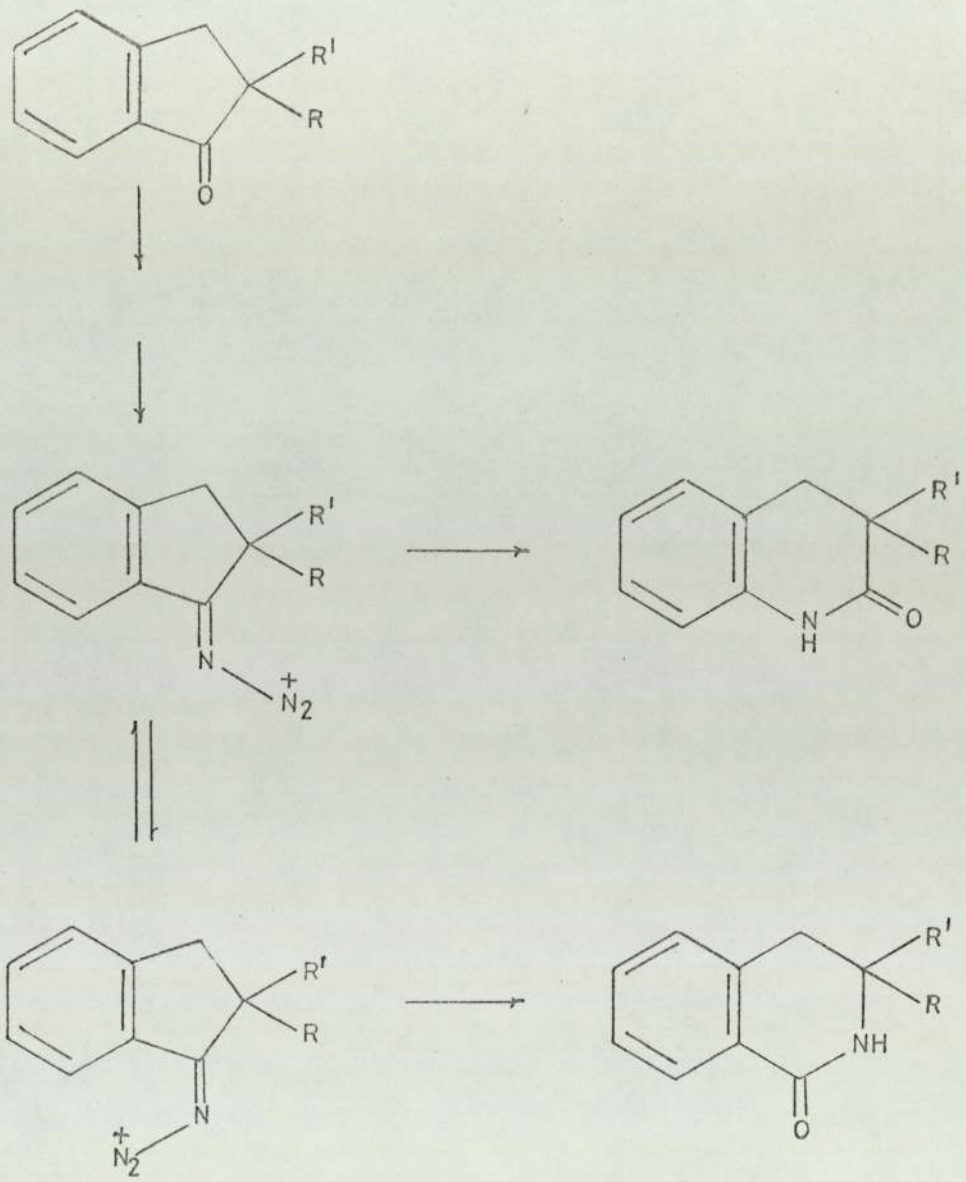
Probably the cis form of the intermediate is the more stable as there is a degree of steric hindrance to the diazonium (N_2^+) group in the

COMPOUND	DETAILS OF U/V SPECTRUM $\lambda_{max.}(\epsilon_{max.})$	INFERENCE
Reference spectra		
(113)	345(1082), 331(1636), 320(1266), 278 (1451), 271(1768).	Quinolone
(114)	302(2779), 265(3959), 224(12000).	Isoquinolone
Experimental spectra		
(95)	288(570), 279(738), 234(6458).	Isoquinolone
(109a)	290(947), 280(1238), 232(8810).	Isoquinolone
(109b)	292(1650), 281(1440), 231(11100).	Isoquinolone
(109c)	325(598), 290(1009), 235(6918).	Isoquinolone
(109d)	287(325), 228(3048).	Isoquinolone
(109e)	287(1037), 279(1250), 232(10000).	Isoquinolone
(116)	338(645), 325(1004), 315(867),283 (2553), 276(2872), 247(6278).	Quinolone
(108a)	345(30), 285(865), 276(1034), 231 (8396).	Isoquinolone
(108b)	340(54), 290(1098), 231(8780).	Isoquinolone
(108c)	290(975), 280(1338), 236(4100).	Isoquinolone
(108d)	286(616), 275(788), 231(7407).	Isoquinolone
(108e)	285(723), 273(964), 236(7879).	Isoquinolone
(96)	291(375), 281(1000), 249(10750).	Isoquinolone

Table 12

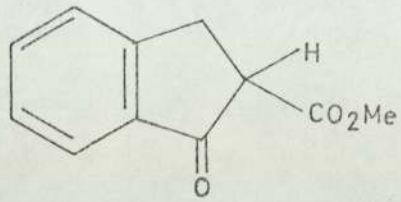
trans form when there is an α-substituent present. Previous work had shown[98,99] that if the α-methylene is unsubstituted the product of the reaction is a quinolone. However, if the α-methylene is substituted this causes steric interaction in the trans intermediate. On the assumption that the energy barrier for interconversion of the isomers is low (that is, interconversion can take place faster than rearrangement), then all the intermediate could revert to the less hindered cis form and the subsequent rearrangement will yield the isoquinolone as the sole product.

A possible explanation as to why compound (116) yields a quinolone arises from an examination of the structure of the intermediate (117). In this case the usually unstable trans

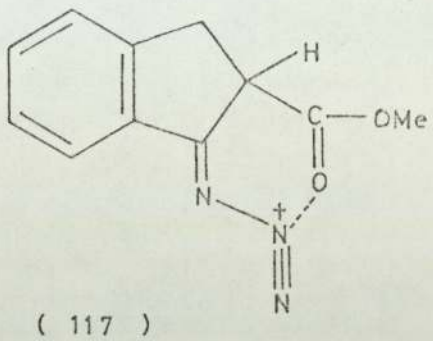


Scheme 15.

intermediate is capable of being stabilised by electrostatic interaction between the positive charge on the nitrogen and the lone pair of electrons on the oxygen.

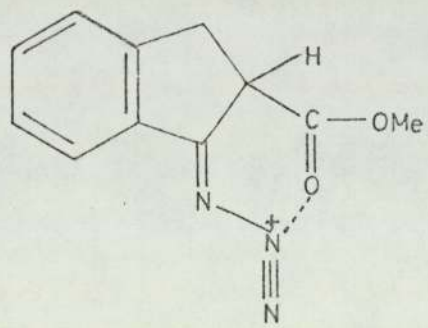


(116)

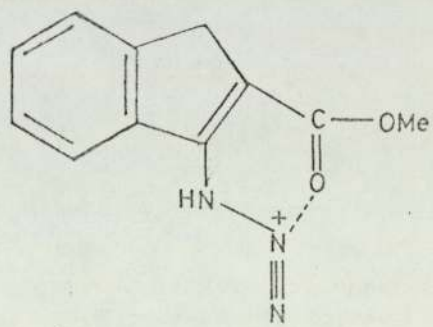


(117)

If this was the only factor involved it would be reasonable to expect that compound (95b) would also give rise to a quinolone. This is not the case, the ring expansion of (95b) yielding only the isoquinolone isomer. However, further stabilisation of the intermediate (117) is possible, in that the intermediate can exist in two tautomeric forms (117a and b). This tautomerism is not possible in the case of the 2-methyl substituted compound (95b).



(117a)

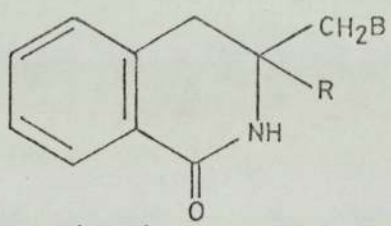


(117b)

Thus, although the trans intermediate of compound (95b) can be stabilised to a certain extent by its ability to form a pseudo 6-membered ring, this increased stability is not sufficient to

outweigh the fact that the cis intermediate has no steric hindrance. In the case of compound (116), however, the trans intermediate is further stabilised by its ability to tautomerise and this may disturb the equilibrium of the two isomers sufficiently to cause the trans isomer to be the more stable and thus cause rearrangement to the quinolone form.

Having demonstrated that the ring-expanded compounds obtained were, with one exception, isoquinolones, the compounds were all submitted to a primary analgetic screen, the qualitative results of which can be seen in Table 13 (more detailed results can be found in Tables 21,22,23,24,25,26,27 in the Pharmacology section).



(108) R = H.

(109) R = Me.

(a) B = dimethylamino.
(b) B = diethylamino.
(c) B = piperidino.
(d) B = morpholino.
(e) B = $\underline{N}^4$-methylpiperazino.

COMPOUND	HOT-PLATE TEST	PHENYLQUINONE TEST
(109a)	Inactive	Negligible activity
(109b)	No results available	No results available
(109c)	Inactive	Moderate activity
(109d)	Moderate activity	Moderate activity
(109e)	No results available	No results available
(108a)	Inactive	Marked activity
(108b)	No results available	No results available
(108c)	Inactive	Inactive
(108d)	Inactive	Marked activity
(108e)	Inactive	Marked activity

Table 13

Again, as in the case of the indanones, comprehensive results are not yet available and so no structure-activity relationships can be postulated. Two generalisations can probably be made, however, from the results at hand. Firstly, the analgetic activity of the compounds which are active manifests itself to a greater extent in the phenylquinone test than in the hot-plate test. The second observation is that the compounds without a methyl substituent in the 2 position appear to have better overall analgetic activity.

Examining the results in more detail, it can be seen that only one compound, (109d), shows any significant activity in the hot-plate test. After administration of (109d) in a dose of 200μM/Kg subcutaneously, reaction times in the hot-plate test increased to 51 seconds, compared with a control time of 35 seconds. An ED_{50} evaluation was carried out, giving a value of 419(220.4-796)μM/Kg which does not compare favourably with the ED_{50} value of 76.8(46-127)μM/Kg for codeine. Three compounds showed some degree of activity in the hot-plate (interaction with morphine) test. This is a test designed to investigate morphine antagonism. At a dose of 50mg/Kg subcutaneously compound (109c) caused a slight reduction in reaction times when administered with morphine (15mg/Kg), although the reduction did not compare favourably with that caused by pentazocine. Compound (108c), at a dose of 200μM/Kg subcutaneously, caused a similar reduction in reaction time in the morphine interaction test. Compound (108e) also caused a reduction in reaction time, which was slightly larger than compounds (109c and 108c) at a dose of 50mg/Kg subcutaneously.

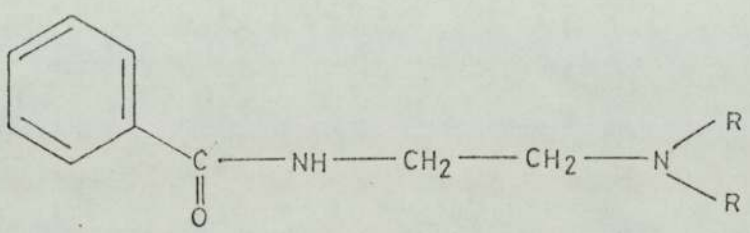
More compounds showed activity in the phenylquinone test than in the hot-plate test. As stated previously, the compounds with the highest analgetic activity are to be found in the series without

the 2-methyl substituent. Compound (109a), at a dose of 400μM/Kg percutaneously, caused 37% inhibition of writhing in the phenylquinone test, compared with 54% inhibition caused by administration of 30μM/Kg of codeine. The corresponding dimethylamino compound in the unsubstituted series, (108a), caused 70% inhibition of writhing at a dose of 100mg/Kg percutaneously. This compares quite favourably with 55% inhibition caused by 10mg/Kg of codeine. Similarly, the morpholino substituted compound (108d) caused 81% inhibition of writhing at a dose of 100mg/Kg, compared with compound (109d) which gave 57% inhibition at a dose of 400μM/Kg. An ED_{50} evaluation of compound (109d) gave a value of 448(incalculable limits)μM/Kg compared with a value of 19(8-45.4)μM/Kg for codeine. The ED_{50} value for compound (108d) of 210(45.7-966)mg/Kg does compare slightly more favourably with a value of 5.7(2.4-13.6)mg/Kg for codeine. The most active compound found was the $\underline{N}^4$-methylpiperazino compound (108e). A dose of 100mg/Kg percutaneously caused 81% inhibition of writhing, but, as yet, no ED_{50} value is available for this compound. One apparent anomaly in this pharmacological study is the activity of compound (109c) in the phenylquinone test, as the corresponding compound (108c) showed no activity at all. A dose of 100mg/Kg of compound (109c) caused 49.1% inhibition of writhing, whereas compound (108c) showed no inhibition of writhing whatsoever. Three compounds from this primary analgetic screen (109c, 108a and e) are currently under investigation in the adjuvant arthritis test.

The original reasoning behind making the benzamide series of compounds more rigid was an attempt to compare the activity of a fairly flexible structure with that of an analogous structure which had a fixed conformation. The model compound (83) which was chosen was unfortunately not attained during the course of this study. However, two series of compounds with fairly close structural

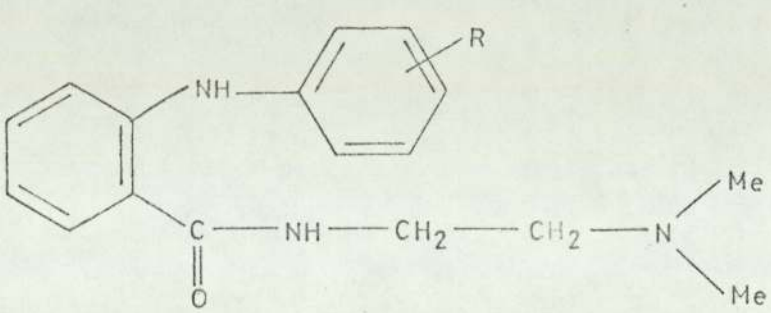
relations were synthesised and tested. A strict comparison between these series of isoquinolones and the original series of benzamides would not, however, be valid as the compounds are not strictly structurally analogous. The general observation can be made, however, that both series of compounds show some degree of analgetic activity. Also it can be said that this activity manifests itself more in the phenylquinone test than in the hot-plate test.

A more meaningful comparison might be made between the series of isoquinolones without the 3-methyl substituent and a series of benzamides with a more flexible structure (118).



(118)

The pharmacology of this type of benzamide has been previously discussed (see section A of Section II). A further point of interest is that of the numerous examples of this type of compound which have been synthesised, only one series of compounds (119) show analgetic activity.



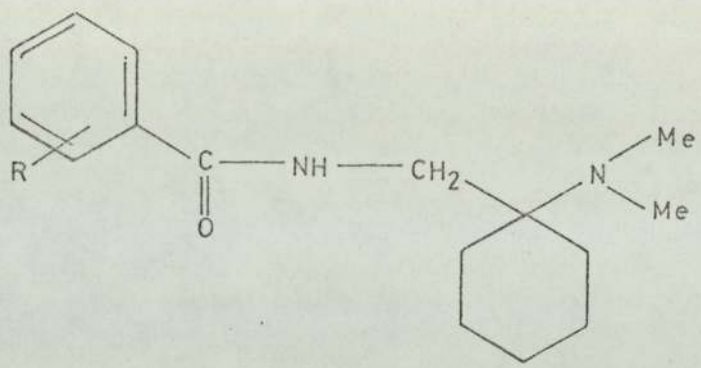
(119)

The majority of the compounds of type (118) appear to be local anaesthetics[54,55,56,57,58]. Thus, it would appear that making the molecule more rigid changes the biological activity from local anaesthesia, acting on the PNS, to analgesia, acting on the CNS. This suggests that the two types of compound are acting by totally different biological mechanisms. Consequently, it appears likely that, if the model series of compounds (83) were synthesised and tested, a valid comparison with the benzamides (118) would not be possible, as the two series of compounds are probably bringing about their biological activity by two different mechanisms.

E: Mass srectrometry

On the basis of the major peaks observed schemes for proposed degradation pathways are suggested although, in some cases, possible minor degradation pathways are also presented. In the more complex spectra some metastable peaks and certain ion fragments are unassigned.

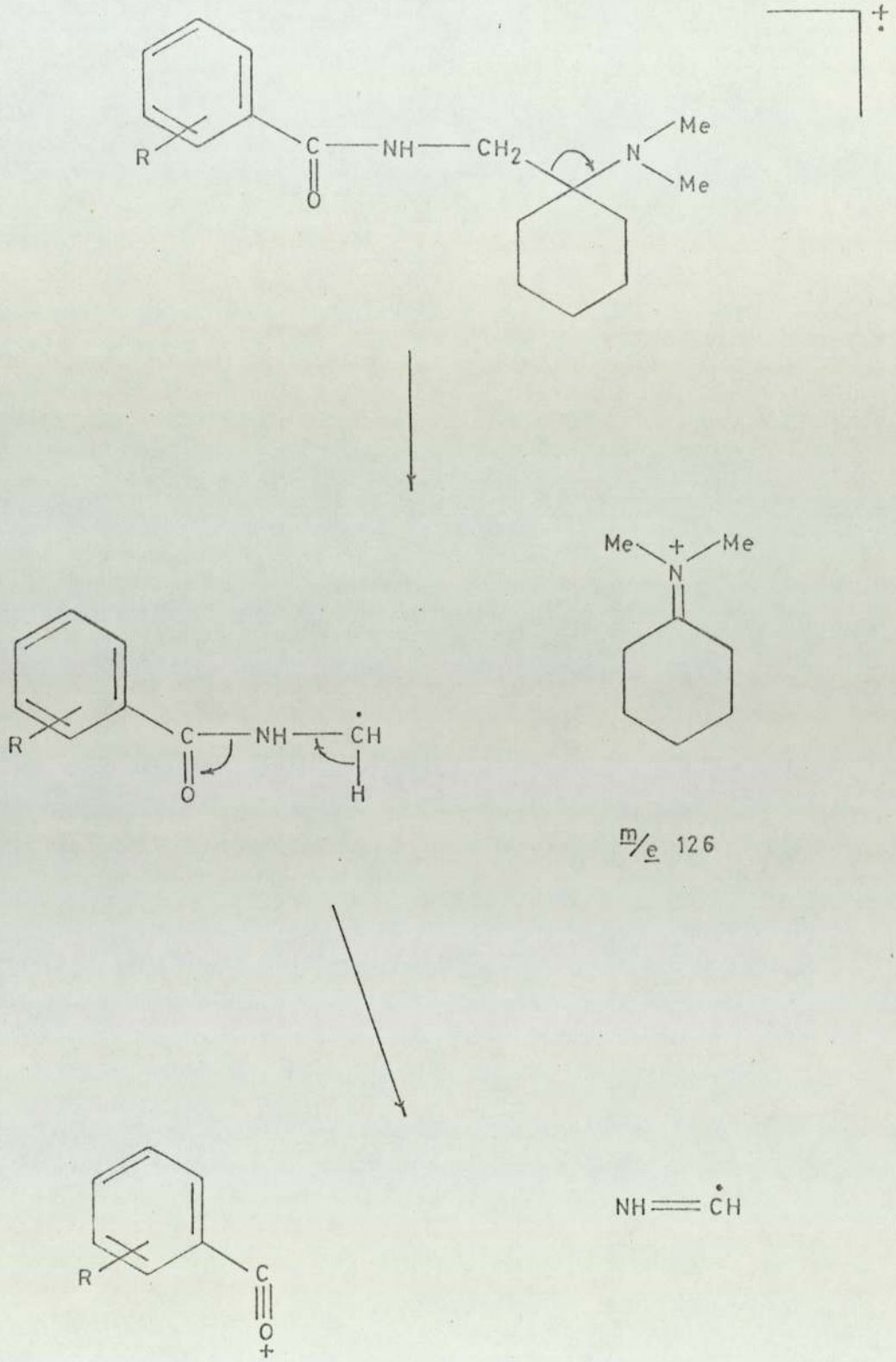
(1) 1-(R-Substituted-benzamidomethyl)-cyclohexyldimethylamines.



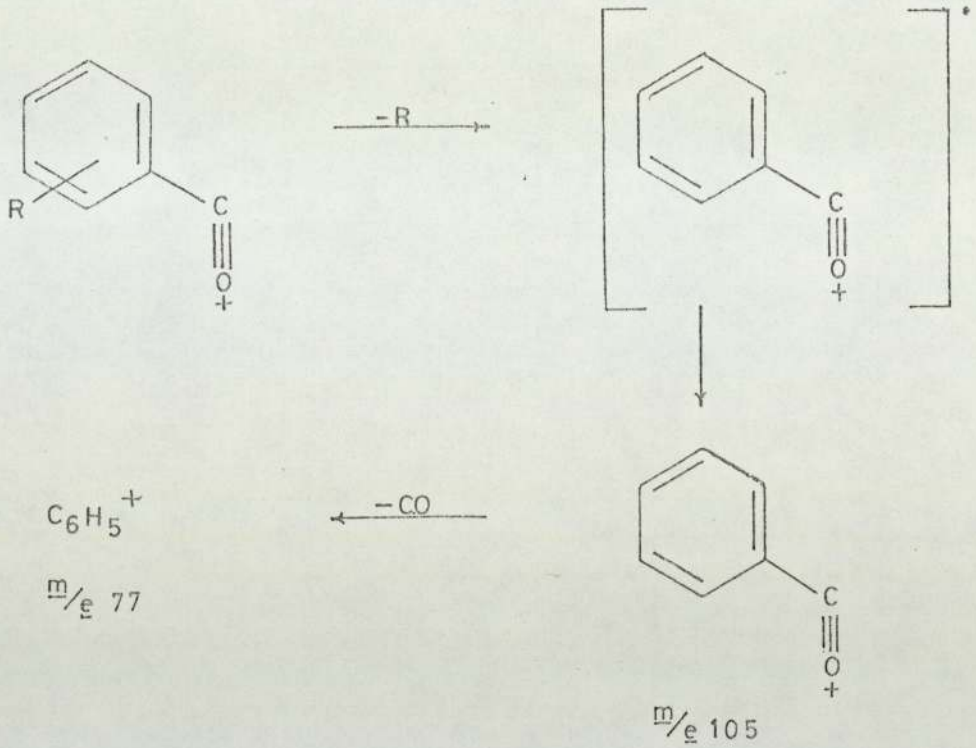
(49)

Mass spectra of these compounds rarely show a molecular ion peak and the molecular ion breaks down as indicated (Scheme 16) to yield the substituted benzoyl cation and a common cation fragment at $^{m}/_{e}$ 126 which is almost invariably the base peak of the spectrum. The substituted benzoyl cation then fragments in the usual manner by initial loss of the substituent R and abstraction of a proton by the fragment ion from the neutral molecule to yield the unsubstituted benzoyl cation $^{m}/_{e}$ 105. This fragment ion then loses carbon monoxide to yield the fragment $C_6H_5^+$, ($^{m}/_{e}$ 77) (Scheme 17).

The common cation fragment $^{m}/_{e}$ 126 abstracts a proton from the neutral molecule to yield the neutral fragment $^{m}/_{e}$ 127. The fragmentation of this ion presents several possibilities (Scheme 18). All the possible pathways commence with α-cleavage of the cyclohexyl ring to yield the radical ion $^{m}/_{e}$ 127. This fission can then

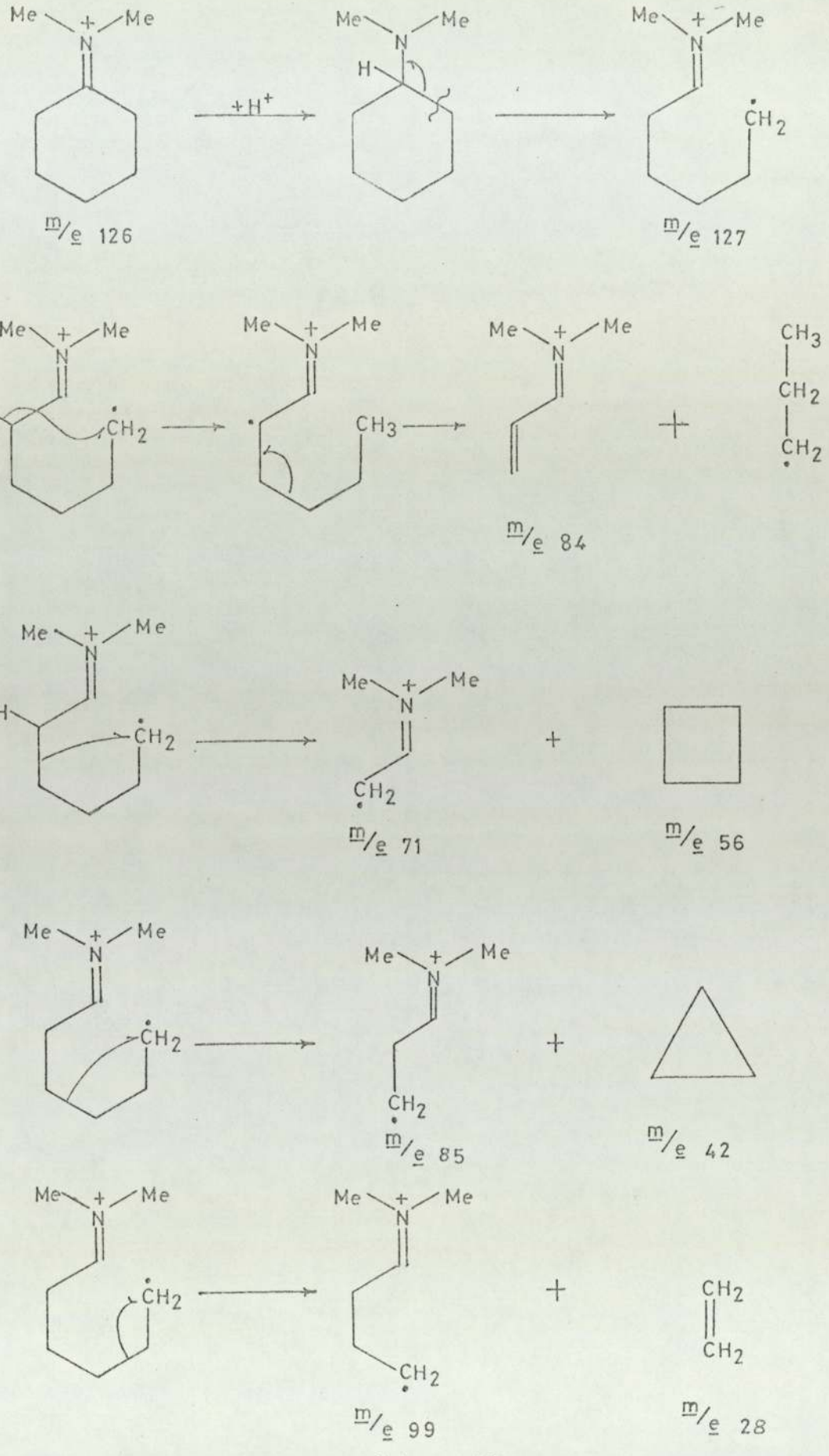


Scheme 16.



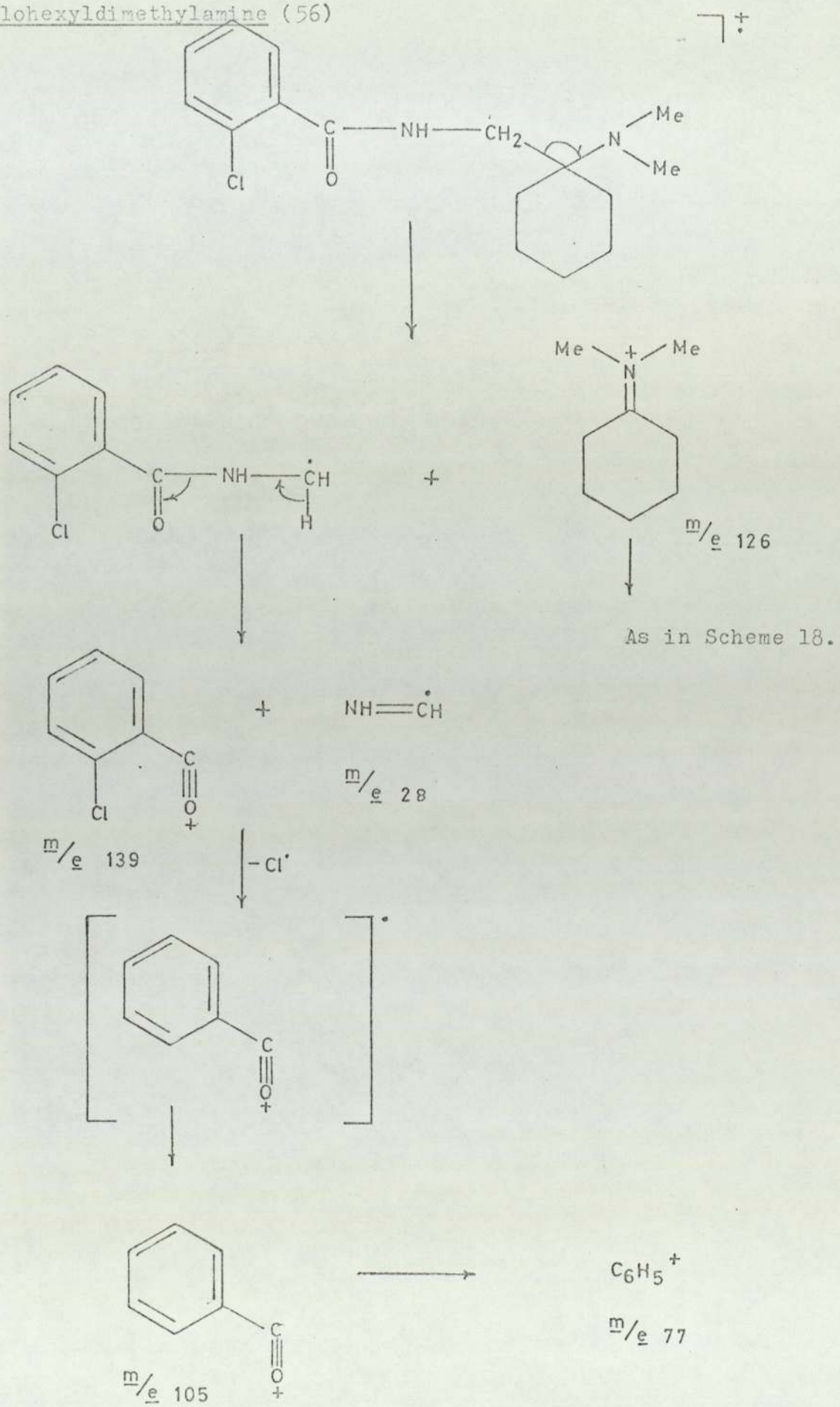
Scheme 17.

be followed by transfer of a hydrogen radical from the 2 position with associated homolysis of the 3-4 bond to yield the fragment ion m/e 84 and a propyl radical m/e 43. Three further pathways could arise by cleavage of the alkyl chain bonds without transfer of a hydrogen radical. Cleavage of the 2-3 bond yields a radical ion m/e 71 and a neutral fragment m/e 56. However, cleavage of the 3-4 bond yields a radical ion m/e 85 and a neutral fragment m/e 42. Finally, cleavage of the 4-5 bond yields a radical ion m/e 99 and a neutral fragment m/e 28.

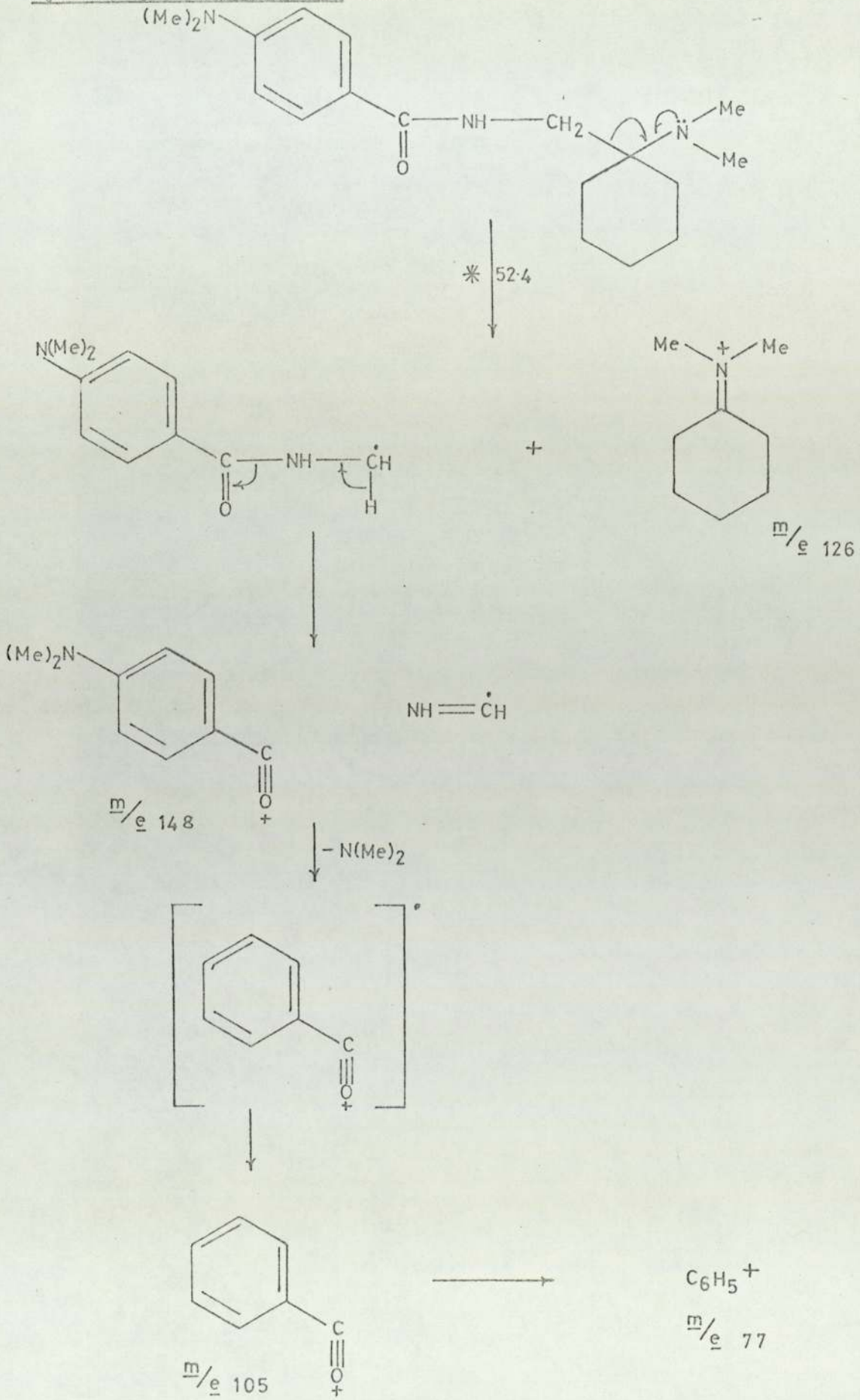

Me
N
Me
+H+
H
CH2
CH3
m/e 126
m/e 127
m/e 84
m/e 71
m/e 56
m/e 85
m/e 42
m/e 99
m/e 28

Scheme 18.

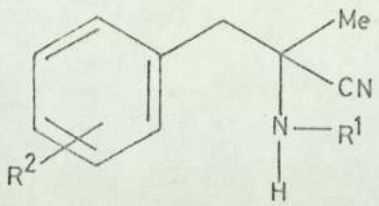
Proposed degradation pathway for 1-(2-chlorobenzamidomethyl)-cyclohexyldimethylamine (56)



Proposed degradation pathway for 1-(4-dimethylaminobenzamidomethyl)-cyclohexyldimethylamine (120)

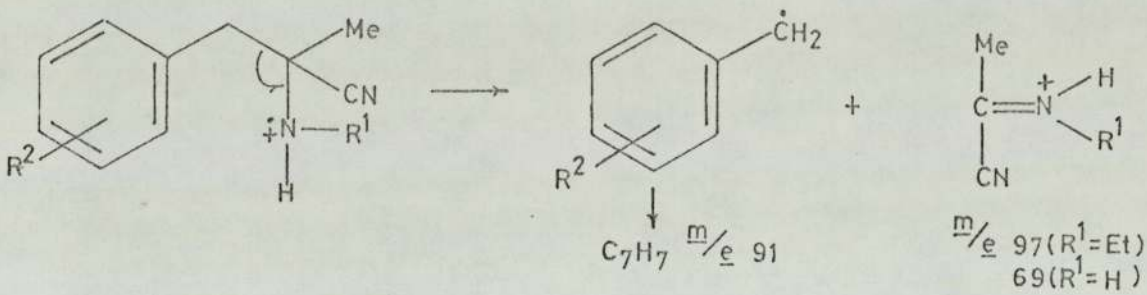


(2) α-Aminonitriles.



(84)

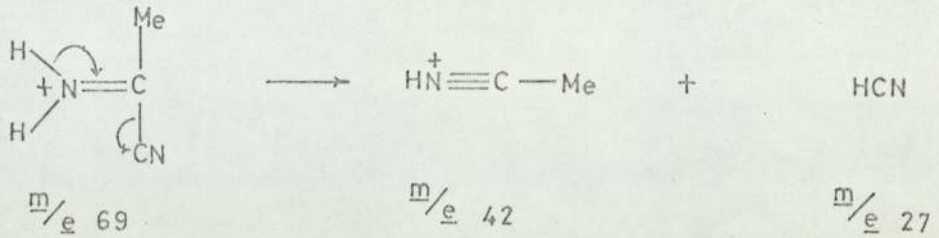
The mass spectra of this series of compounds do not show a molecular ion peak but α-fission takes place immediately as shown in Scheme 19.



Scheme 19.

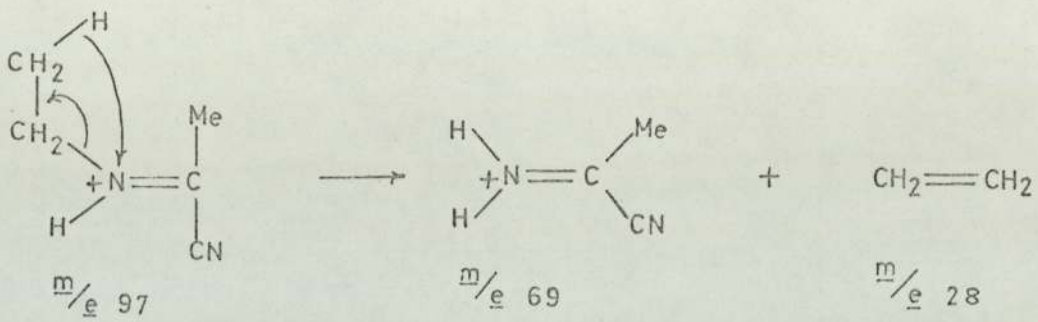
The radical thus produced loses the substituent R^2 to form the tropylium ion $^{m}/_{e}$ 91. The proposed degradation of the cation depends upon the substituent R^1. If R^1 = H then the original fragmentation of the molecule would produce a cation $^{m}/_{e}$ 69. This ion could then expel hydrogen cyanide to yield a cation $^{m}/_{e}$ 42 (Scheme 20). If R^1 = ethyl then the original fragmentation of the molecule would produce a cation $^{m}/_{e}$ 97. Fission of the C-N bond on the opposite side from the original cleavage with hydrogen rearrangement is then possible, producing an ion $^{m}/_{e}$ 69 and

expelling ethylene (Scheme 21).



m/e 69 m/e 42 m/e 27

Scheme 20.



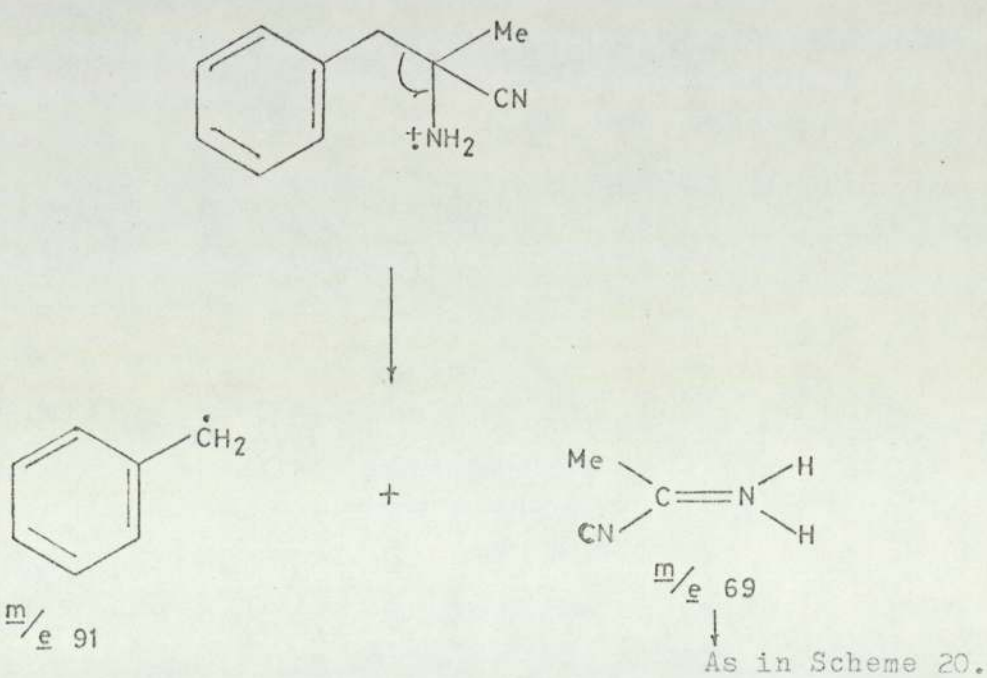
m/e 97 m/e 69 m/e 28

Scheme 21.

The ion so produced can then fragment as in Scheme 20.

In all cases, whether the amine is primary or secondary, a small peak at M-27 is observed which corresponds to the loss of hydrogen cyanide.

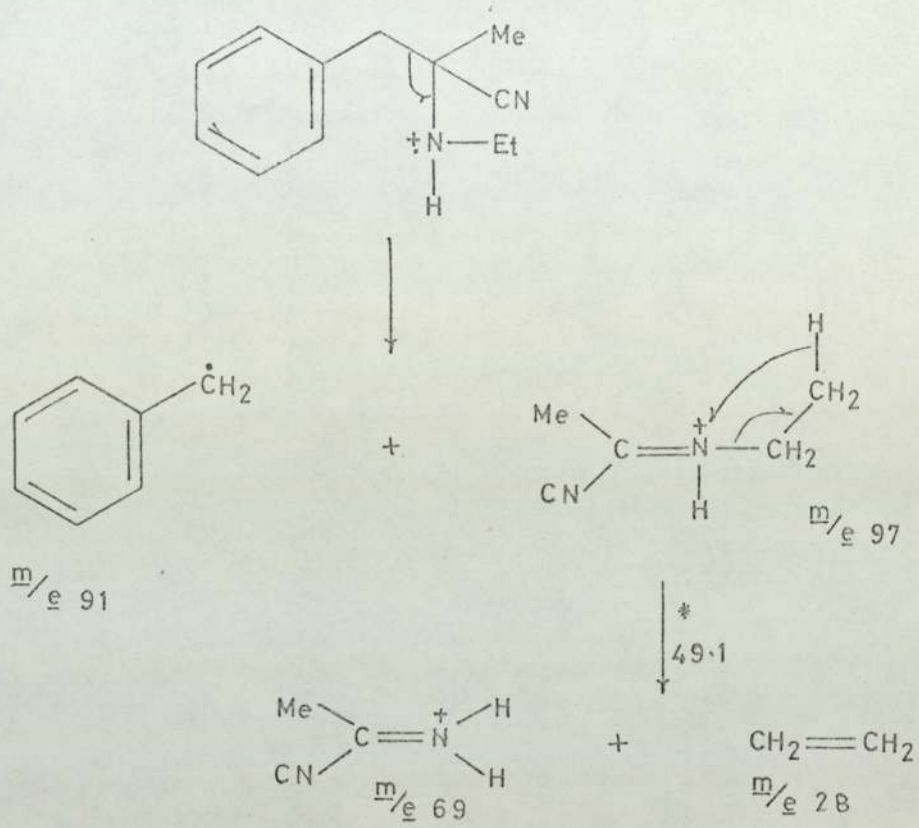
Proposed degradation pathway of 2-amino-2-methyl-3-phenylpropanonitrile (87a)



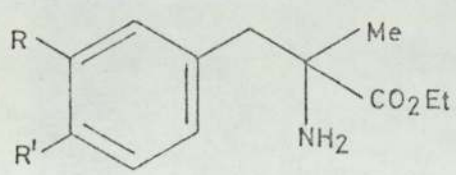
m/e 91 m/e 69

As in Scheme 20.

Proposed degradation pathway of 2-ethylamino-2-methyl-3-phenyl-propanonitrile (84a)



(3) α-Aminoesters.



(a) R = R' = H.

(b) R = R' = OMe.

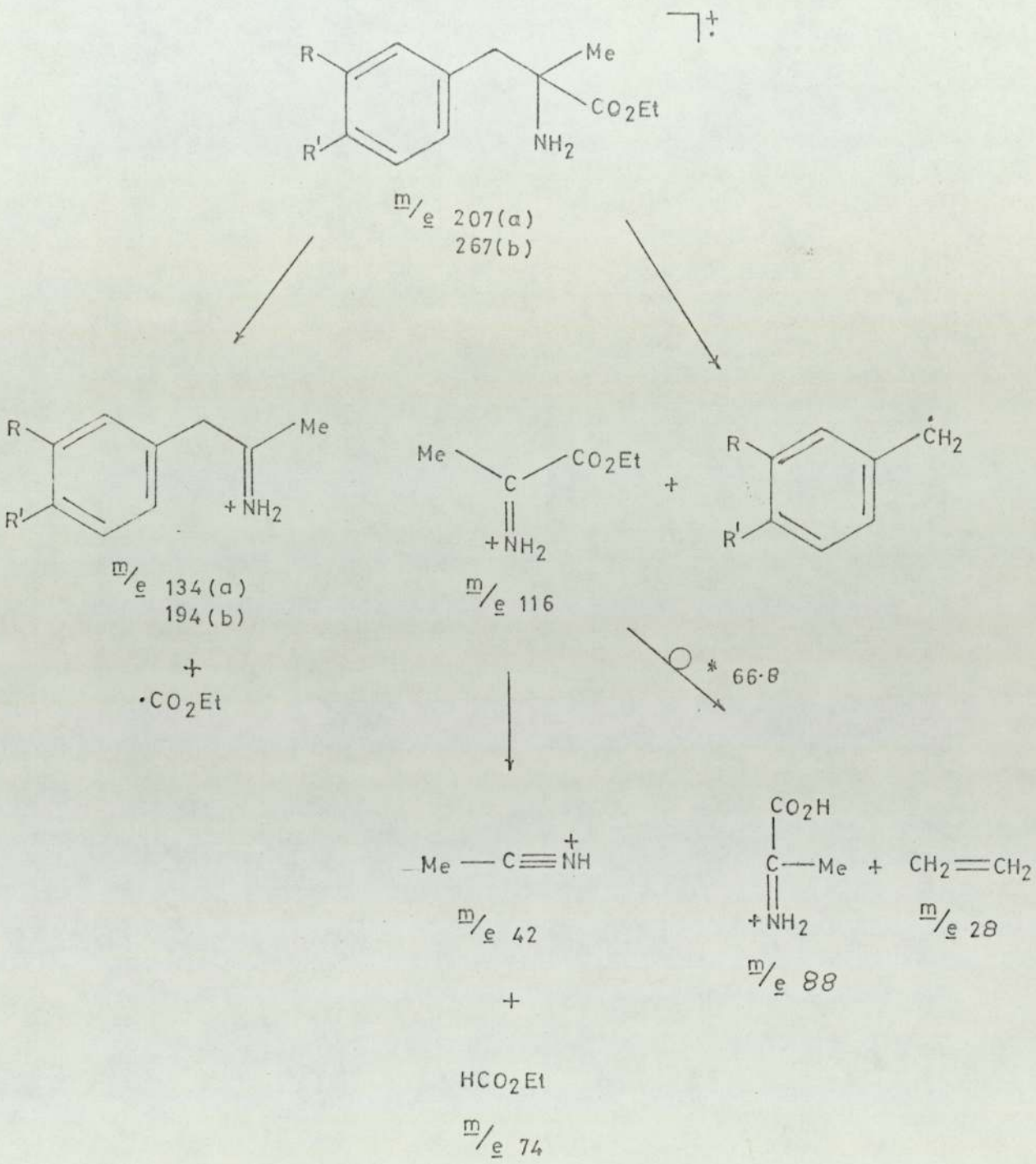
(89)

Only two compounds of this type were prepared and the mass spectra of both showed a base peak at m/e 116. This was derived by α-fission of the molecular ion in a manner analogous to the

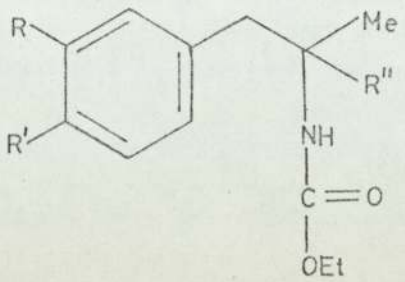
α-aminonitriles (see Scheme 19). This type of fission produced the same cation fragment, $\frac{m}{e}$ 116, in both cases, together with the appropriately substituted tropylium radical. The ion fragment $\frac{m}{e}$ 116 could then undergo a McLafferty rearrangement, losing a molecule of ethylene to form the cation $\frac{m}{e}$ 88. The ion fragment $\frac{m}{e}$ 116 could also lose a molecule of ethyl formate to yield the cation $\frac{m}{e}$ 42.

Another possible fragmentation of the molecular ion would be the loss of a carbethoxyl radical to leave the appropriate cation, $\frac{m}{e}$ 134 in the case of (a) and $\frac{m}{e}$ 194 in the case of (b).

Proposed degradation pathway for 2-amino-2-methyl-3-(substituted-phenyl)-propanoic acid ethyl esters (89a and b)



(4) Urethans.

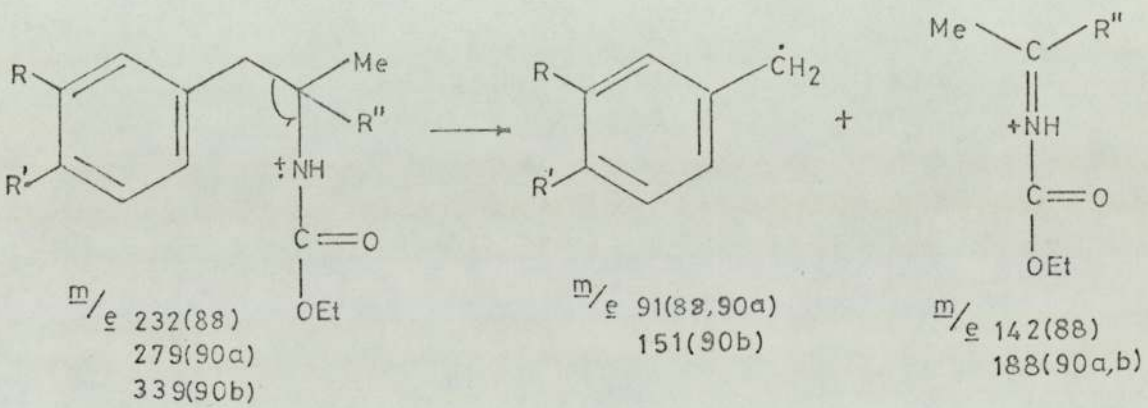


(88) R = R' = H, R'' = CN.

(90a) R = R' = H, R'' = COOEt.

(90b) R = R' = OMe, R'' = COOEt.

In all three compounds the two major peaks in the spectra were produced by the normal α-fission (Scheme 22) as discussed in the previous two sections.

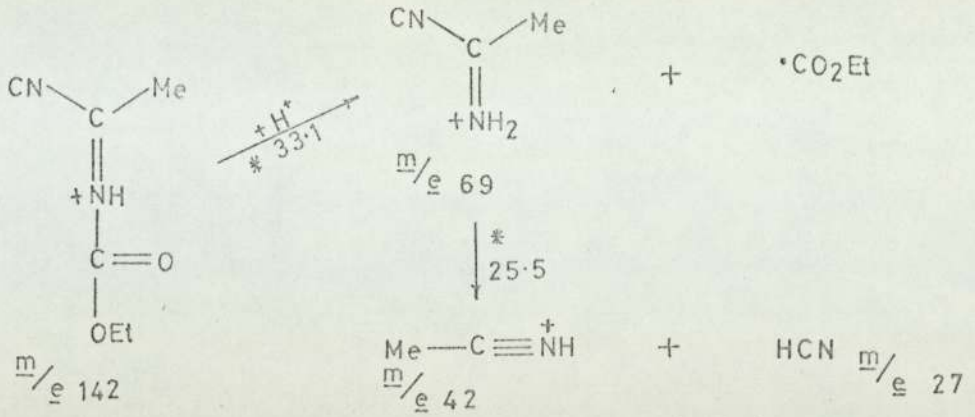


Scheme 22.

In the aminonitrile (88), the cation $^{m}/_{e}$ 142 produced could lose a carbethoxyl radical, $^{m}/_{e}$ 73, to produce the ion fragment $^{m}/_{e}$ 69 (Scheme 23), after having abstracted a proton from the neutral molecule. This ion fragment $^{m}/_{e}$ 69 could then lose a molecule of hydrogen cyanide to yield the ion $^{m}/_{e}$ 42.

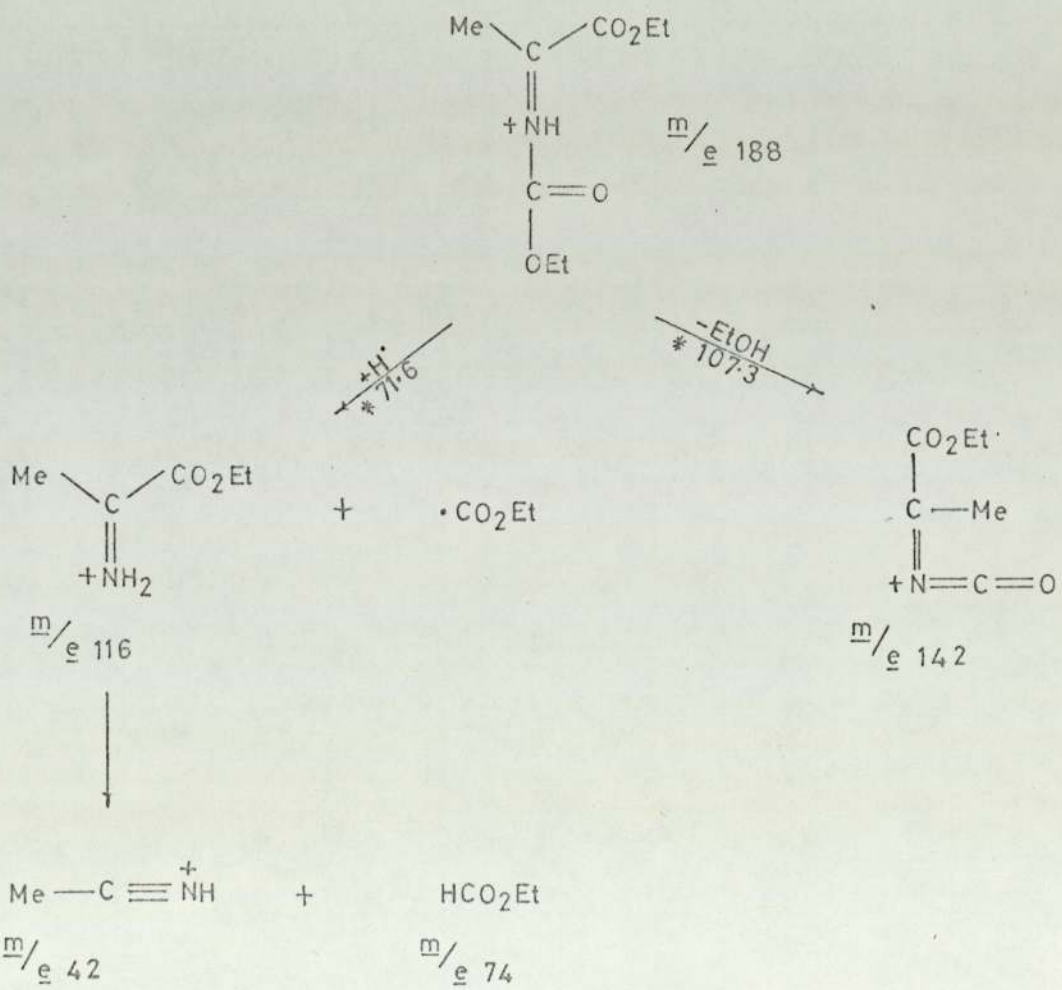
In the aminoesters (90a and b) the ion produced by the original fission, $^{m}/_{e}$ 188, could fragment by two possible routes (Scheme 24), one route by loss of a carbethoxyl radical and abstraction of a proton to yield an ion $^{m}/_{e}$ 116 and then loss of ethyl formate to produce an ion fragment $^{m}/_{e}$ 42, and the other

route by elimination of ethanol to yield the isocyanate m/e 142.



Scheme 23.

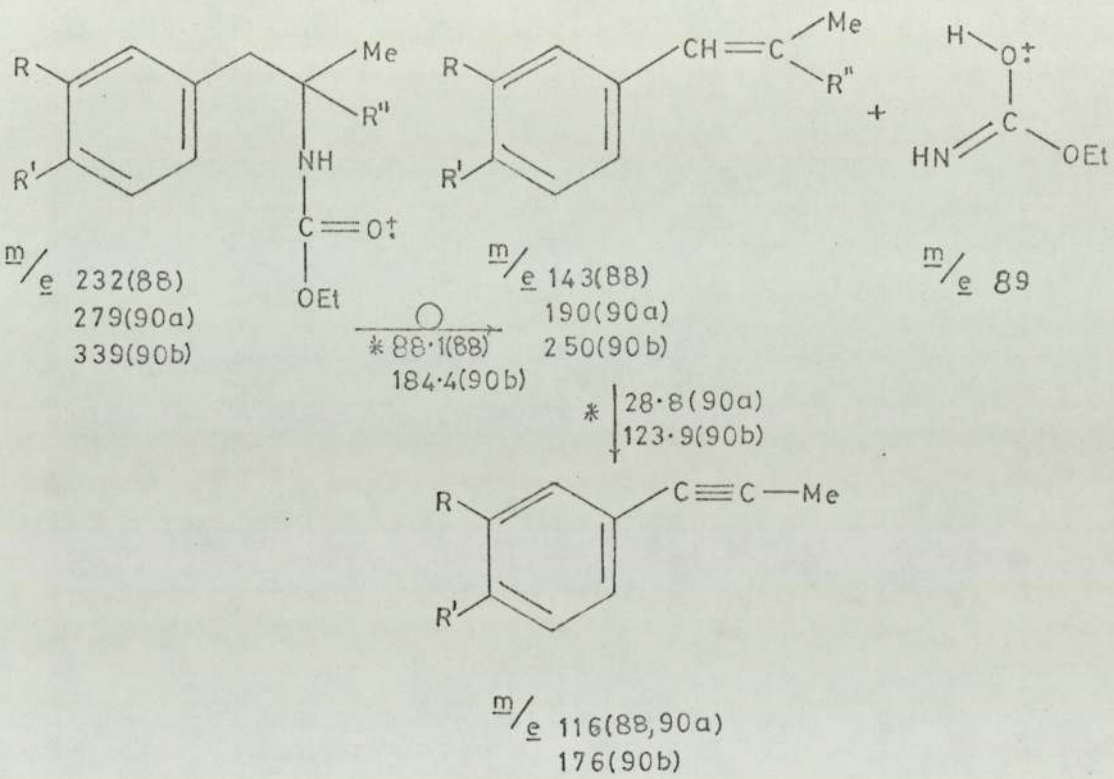
This elimination of ethanol has previously been observed in the spectra of urethans[100,101,102] and is diagnostically important, since this pathway is unavailable to N,N-disubstituted urethans.



Scheme 24.

The ion fragment $^{m}/_{e}$ 116 produced in Scheme 24 can also undergo a McClafferty rearrangement, as previously discussed in the section on α-aminoesters, thus eliminating a molecule of ethylene to produce the ion $^{m}/_{e}$ 88.

Another possible fragmentation pathway which is common to all three compounds is a McLafferty rearrangement of the molecular ions (Scheme 25).



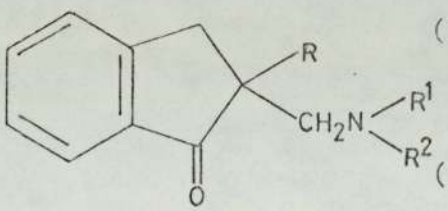
Scheme 25.

In all cases this produced the ion $^{m}/_{e}$ 89. In the α-aminonitrile (88) a neutral fragment $^{m}/_{e}$ 143 was produced which could then lose a molecule of hydrogen cyanide to produce the neutral fragment $^{m}/_{e}$ 116. This same neutral fragment could be produced in the α-aminoesters (90a and b) by loss of ethyl formate from the neutral fragment resulting from the original McLafferty rearrangement.

Another possible loss of ethyl formate could be from the molecular ion to yield peaks at $^{m}/_{e}$ 158 (a), $^{m}/_{e}$ 205 (b) and $^{m}/_{e}$ 265 (c), although no indication could be given as to which carbethoxyl group would be lost.

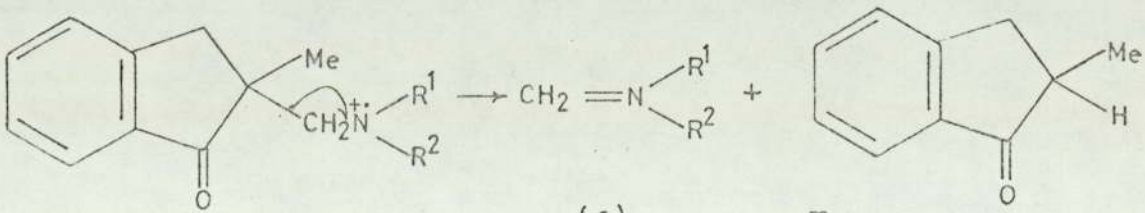
(5) Indanones.

The indanones can be subdivided into those which are 2-substituted and those which are 2,2-disubstituted. Both types of compound show a small peak corresponding to the molecular ion but subsequent fragmentation varies according to the substitution in the 2 position. In the 2,2-disubstituted compounds (105b) it would appear that the first fragmentation is a simple α-fission (Scheme 26) to yield the fragment ion (c) and a radical $^{m}/_{e}$ 145 which can then abstract a proton from the neutral molecule to yield the neutral fragment $^{m}/_{e}$ 146.



(105a) R = H, R^1 = R^2 = various

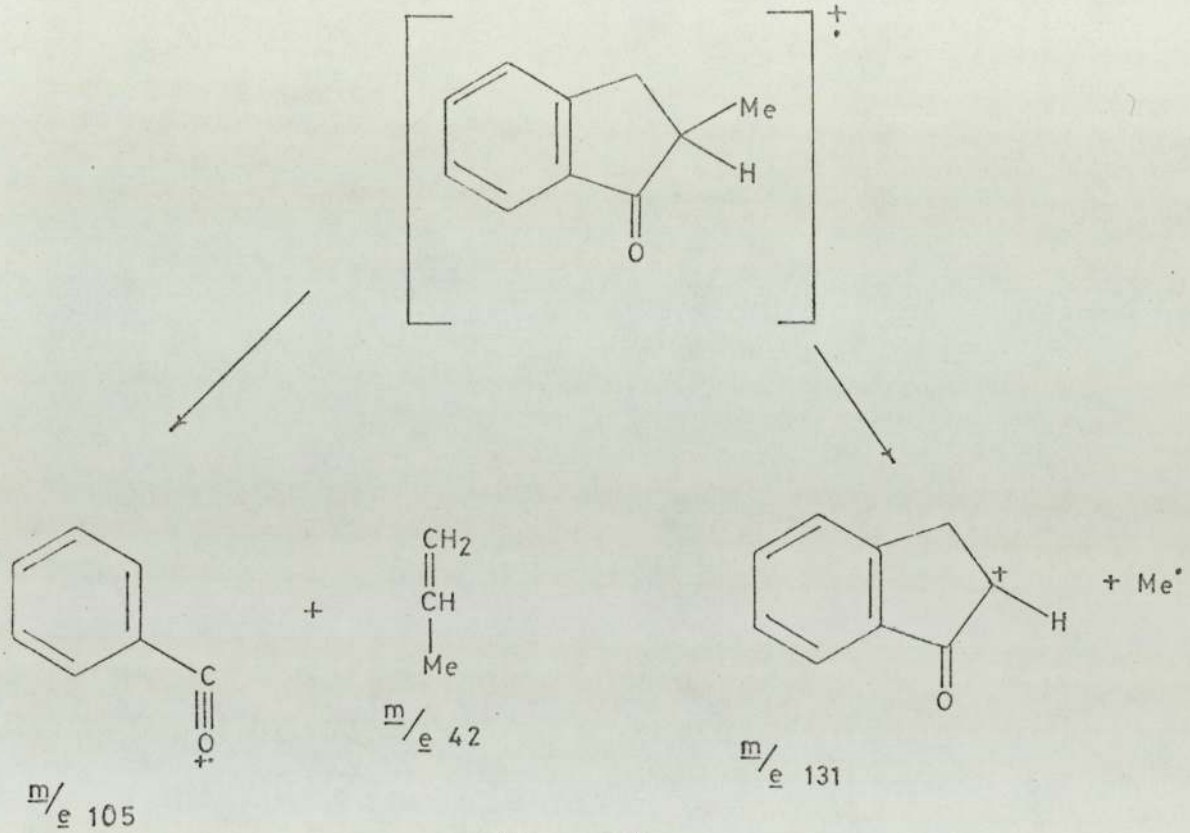
(105b) R = Me, R^1 = R^2 = various



$^{m}/_{e}$ 146

Scheme 26.

This fragment could further break down by two routes (Scheme 27). The first route involves loss of a methyl radical to yield the fragment $^{m}/_{e}$ 131. The second involves formation of the acylium ion by loss of prop-1-ene and H· transfer. The acylium ion can then form the C_6H_5 ($^{m}/_{e}$ 77) fragment by loss of carbon monoxide.

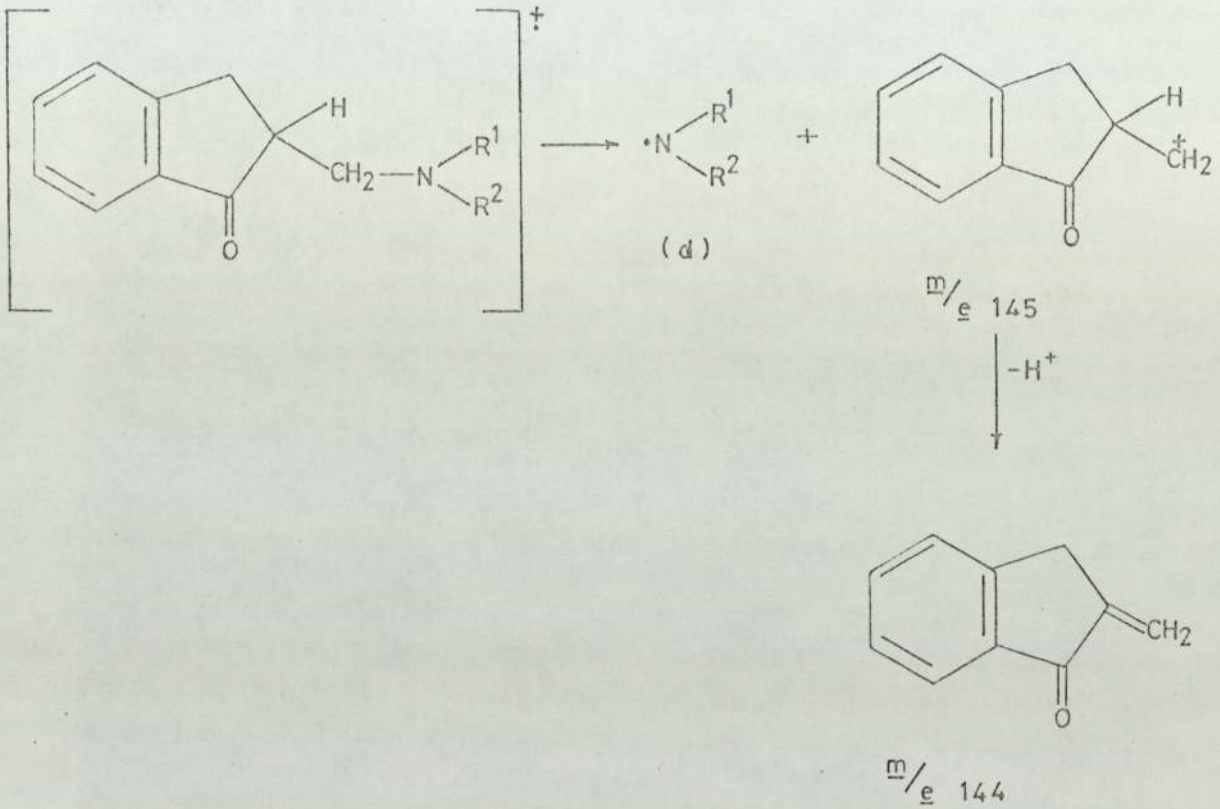


Scheme 27.

In all the spectra of the 2,2-disubstituted indanones the base peak corresponds to the fragment ion (c) produced by the initial α-fission. In addition, all the spectra show a fairly large peak at $^{m}/_{e}$ 116. The source of this peak has not been determined but it has been shown, by metastable determination, to lose H· to yield a peak at $^{m}/_{e}$ 115.

In the spectra of the 2-substituted indanones a difference in the initial fragmentation appears to be caused by the lack of a

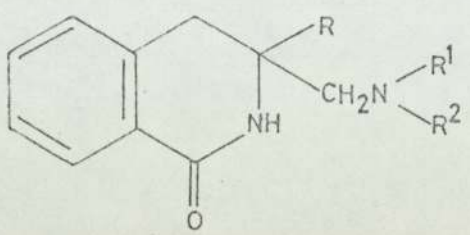
methyl substituent in the 2 position. The initial loss appears to be an amine radical (d) to yield an ion $^{m}/_{e}$ 145 followed by loss of a proton to yield the neutral fragment $^{m}/_{e}$ 144 (Scheme 28).



Scheme 28.

Although the amine fragment forms the base peak of the spectrum in most cases, an α-fission similar to that in Scheme 26 also appears to take place to varying extents, yielding the radical $^{m}/_{e}$ 131 and the appropriate cation. The peak $^{m}/_{e}$ 116 is also present in the spectra of 2-substituted indanones, but in this case it can be shown, by metastable determination, to arise from a neutral fragment $^{m}/_{e}$ 144 by loss of carbon monoxide. Again, as in the case of 2,2-disubstituted indanones, metastable determinations show that this C_9H_8 fragment loses H$^{\cdot}$ to yield the C_9H_7 fragment $^{m}/_{e}$ 115.

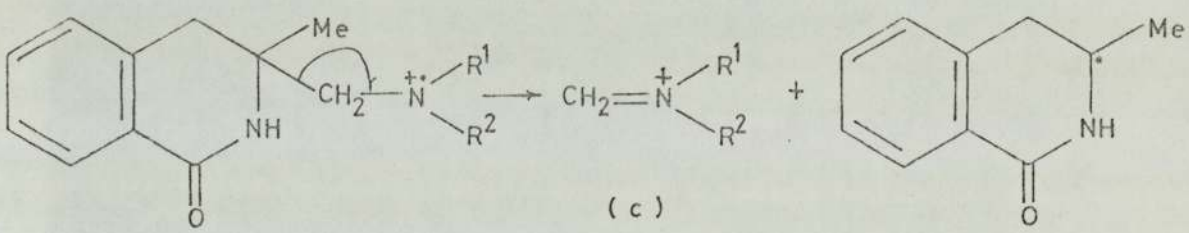
(6) Isoquinolones.



(108) R = H, R^1 = R^2 = various

(109) R = Me, R^1 = R^2 = various

In the 3,3-disubstituted isoquinolones (109), the initial fragmentation appears to be a simple α-fission in a manner analogous to that in the 2,2-disubstituted indanones (Scheme 29).



(c)

Scheme 29.

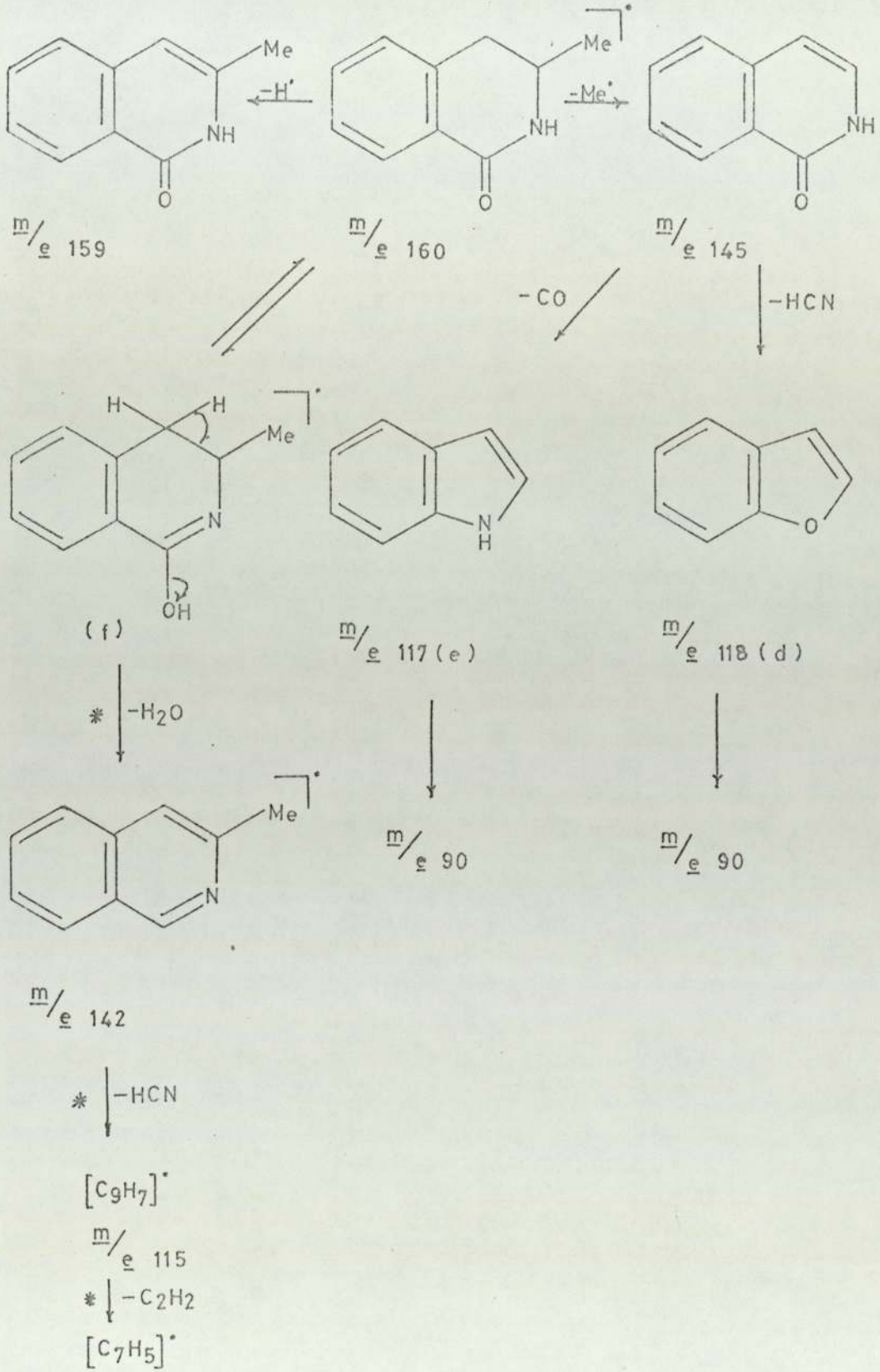
This gives rise to the common radical $^{m}/_{e}$ 160 together with the appropriate cation (c). The radical $^{m}/_{e}$ 160 can then further fragment by several routes (Scheme 30). Loss of a hydrogen radical could give rise to the neutral fragment $^{m}/_{e}$ 159. Loss of a methyl radical accompanied by hydrogen ion transfer could give rise to the neutral fragment $^{m}/_{e}$ 145. The fragmentation of this latter type of structure has been previously reported[103] and the two main routes are loss of hydrogen cyanide to yield (d) followed by loss of carbon monoxide to yield the fragment $^{m}/_{e}$ 90, and a route that

involves initial loss of carbon monoxide to yield (e) followed by loss of hydrogen cyanide to yield the fragment $^{m}/_{e}$ 90. It was reported[103] that the major route was loss of hydrogen cyanide followed by loss of carbon monoxide, with the two losses in reverse order being only a minor route. This does not, however, appear to be the case in the spectra of the isoquinolones examined so far, the two routes being of approximately equal significance.

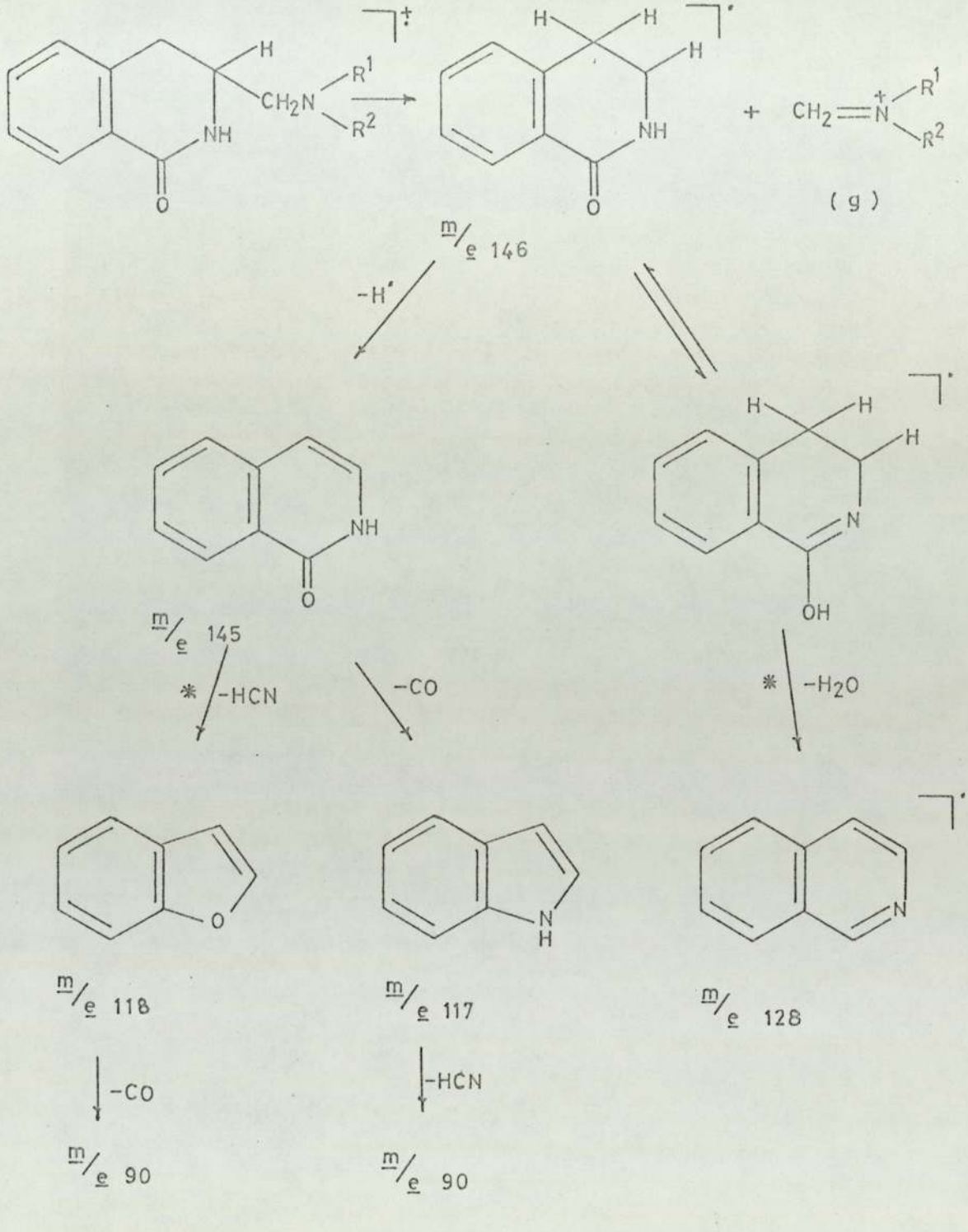
If the fragment $^{m}/_{e}$ 160 is drawn in its tautomeric form (f), it becomes more apparent that loss of water can take place to yield $^{m}/_{e}$ 142 and this has been shown to occur by metastable determination. The radical $^{m}/_{e}$ 142 thus formed has also been shown, by metastable determination, to lose hydrogen cyanide to yield $(C_9H_7)^{\cdot}$ $^{m}/_{e}$ 115 which subsequently loses C_2H_2 to yield $(C_7H_5)^{\cdot}$ $^{m}/_{e}$ 89.

In the 3-substituted isoquinolones (108) examined, as in the 2-substituted indanones, the initial fragmentation can take place by two possible routes (Schemes 31 and 32). As in the 3,3-di-substituted isoquinolones (109), α-fission can take place to yield the common radical $^{m}/_{e}$ 146 and the appropriate cation (g). Loss of H$^{\cdot}$ from the radical $^{m}/_{e}$ 146 gives rise to the neutral fragment $^{m}/_{e}$ 145 which can then fragment as previously shown in Scheme 30. By means of metastable determination, loss of water from the radical $^{m}/_{e}$ 146 has been shown to occur (Scheme 31).

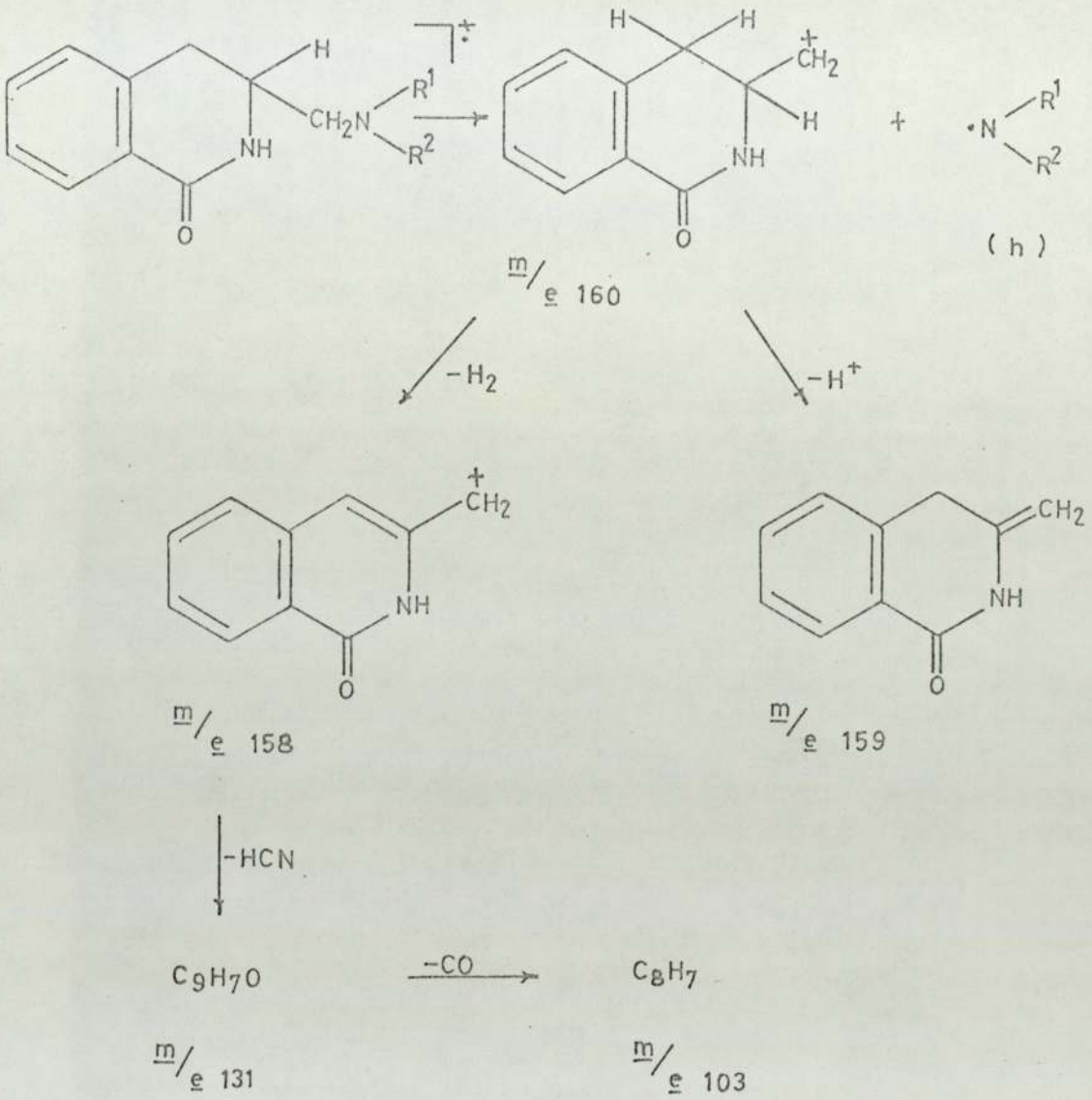
The second type of fragmentation of the molecular ion (Scheme 32) is loss of the appropriate amine radical (h) followed by loss of a proton to yield the fragment $^{m}/_{e}$ 159. It is then possible for the fragment $^{m}/_{e}$ 160 to lose hydrogen to yield the ion $^{m}/_{e}$ 158, from which hydrogen cyanide loss (to $^{m}/_{e}$ 131) followed by carbon monoxide loss (to $^{m}/_{e}$ 103) is possible.


Me
-H·
NH
O
m/e 159
Me
-Me·
NH
O
m/e 160
NH
O
m/e 145
-CO
-HCN
H
H
Me
N
OH
(f)
* -H2O
N
H
m/e 117 (e)
O
m/e 118 (d)
Me
N
m/e 142
* -HCN
[C9H7]·
m/e 115
* -C2H2
[C7H5]·
m/e 90
m/e 90

Scheme 30.



Scheme 31.


H
CH2N
R1
R2
NH
O
+·
H
H
CH2
H
NH
O
+
·N
R1
R2
(h)
m/e 160
-H2
-H+
CH2
NH
O
m/e 158
CH2
NH
O
m/e 159
-HCN
C9H7O
-CO
C8H7
m/e 131
m/e 103

Scheme 32.

SECTION III

EXPERIMENTAL

Determination of Equivalent Weights

The equivalent weights of bases were determined by titration with 0.1N perchloric acid in acetic acid using Oracet Blue B indicator. Titration of the hydrohalide and quaternary salts was carried out in the same solvent in the presence of 3% mercuric acetate.

Preparation of Hydrochloride salts

The base was dissolved in a 10% $^{w}/_{v}$ solution of hydrochloric acid in ethanol, the ethanol evaporated and the residue crystallised from ethanol/ether unless otherwise indicated.

Infrared absorption spectra

Infrared spectra were recorded using a Unicam S.P. 200 spectrophotometer. The samples were run as liquid films, mulls in liquid paraffin or as solutions in chloroform. Some unassigned peaks are also recorded.

Nuclear Magnetic Resonance Spectra

Nuclear magnetic resonance spectra were determined in deutero-chloroform, carbon tetrachloride, trifluoroacetic acid and D_2O on a Varian A60 spectrometer using tetramethyl silane as an internal standard. All the peaks were assigned in τ values.

Mass spectra

Mass spectra were measured with an A.E.I. MS9 spectrometer (ionising voltage 70 eV, trap current 100μA, accelerating voltage 8kV). Samples were introduced through the heated inlet system at 150°.

Melting points

Melting points were determined using an Electrothermal melting point apparatus. Melting points are uncorrected.

Microanalyses

Microanalyses were carried out by Strauss Laboratories, Oxford.

A: DERIVATIVES OF CYCLOHEXYLDIMETHYLAMINE

1-Cyanocyclohexyldimethylamine (47)

A solution of dimethylamine hydrochloride (40.75g) in water ($75cm^3$) was added to cyclohexanone (49.0g), quickly followed by a solution of potassium cyanide (34.0g) in water ($75cm^3$), added over 5min. The mixture was stirred for 24hr at room temperature during which time a crystalline solid was formed. The solid was filtered, washed with ice-cold water ($100cm^3$), dissolved in benzene ($75cm^3$) and rewashed with water ($50cm^3$). The aqueous layer was extracted with benzene ($100cm^3$), the benzene solutions combined, dried ($MgSO_4$) and evaporated under reduced pressure to yield a colourless oil which, on standing, yielded colourless prisms of 1-cyanocyclohexyldimethylamine (60.8g, 80.0%; lit. 51.4g, 62.4%), m.p. 32° (lit. b.p. 88°/3.5 mm), $\nu_{max.}$ (nujol), 2250 (C≡N), 1245, 1160, 1080, 1040, 1000, 985, 885, 815cm^{-1}.

1-Aminomethylcyclohexyldimethylamine (48)

1-Cyanocyclohexyldimethylamine (15.2g) was dissolved in dry ether ($150cm^3$) and added dropwise to a stirred suspension of lithium aluminium hydride (7.6g) in dry ether ($150cm^3$). The suspension was stirred overnight and excess lithium aluminium hydride decomposed by dropwise addition of water ($12cm^3$). The ether layer was separated, dried ($MgSO_4$) and evaporated to yield a yellow, mobile oil (11.6g, 74.3%; lit. 14.3g, 92.5%). Addition of 10% ethanolic hydrochloric acid to an ethereal solution of the oil gave a solid which was recrystallised from ethanol/ether as colourless needles of 1-aminomethylcyclohexyldimethylaminedihydrochloride, m.p. 251-3° (lit. 251-3°), $\nu_{max.}$ (nujol), 3350 (NH), 2600-2400 (NH^+), 1270, 1200, 1160, 1050, 990, 820cm^{-1}.

1-(2-Chlorobenzamidomethyl)-cyclohexyldimethylamine (56)

A mixture of 1-aminomethylcyclohexyldimethylamine (1.5g), 2-chlorobenzoyl chloride ($3cm^3$) and pyridine ($7cm^3$) was allowed to stand at room temperature for 1hr. The white solid (2.1g, 63.8%) produced was filtered and recrystallised from ethanol to yield colourless prisms of 1-(2-chlorobenzamidomethyl)-cyclohexyldimethylamine-hydrochloride, m.p. 228-9° (Found: C,58.01; H,6.95; N,8.46; equiv., 336.0. $C_{16}H_{24}Cl_2N_2O$ requires C,57.89; H,7.13; N,8.40%; equiv., 331.0), $\nu_{max.}$ (nujol), 3160 (NH); 2670-2500 (NH^+), 1655 (amide CO), 1590, 1555, 1440, 1310, 1140, 750 (Ph)cm^{-1}.

τ (D_2O) 8.20 (10H, m, cyclohexyl-CH_2's), 7.10 (6H, s, $(CH_3)_2N^+$), 6.15 (2H, s, NH-CH_2), 2.50 (4H, m, aromatic H's).

1-Cinnamamidomethylcyclohexyldimethylamine (57)

A mixture of 1-aminomethylcyclohexyldimethylamine (1.0g), cinnamoyl chloride ($2cm^3$) and pyridine ($7cm^3$) was allowed to stand at room temperature for 1hr. The white solid (2.2g, 70.9%) produced was filtered and recrystallised from ethanol to yield colourless prisms of 1-cinnamamidomethylcyclohexyldimethylaminehydrochloride, m.p. 214-5° (Found: C,66.99; H,8.51; N,8.59; Cl,10.74; equiv., 326.6. $C_{18}H_{27}ClN_2O$ requires C,66.98; H,8.37; N,8.68; Cl,11.01%; equiv., 322.5), $\nu_{max.}$ (nujol), 3180 (NH), 2600-2500 (NH^+), 1665 (amide CO), 1630 (C=C), 1560, 1340, 1220, 1135, 970, 770, 750 (Ph)cm^{-1}.

τ (D_2O) 8.40 (10H, m, cyclohexyl-CH_2's), 7.20 (6H, s, $(CH_3)_2N^+$), 6.40 (2H, s, NH-CH_2), 3.55 (1H, d, CH-CO), 3.25 (1H, d, Ph-CH), 2.50 (5H, m, aromatic H's).

1-(4-Nitrobenzamidomethyl)-cyclohexyldimethylamine (58)

A mixture of 1-aminomethylcyclohexyldimethylamine (1.0g), 4-nitrobenzoyl chloride ($2cm^3$) and pyridine ($7cm^3$) was allowed to stand at room temperature for 1hr. The white solid (2.08g, 63.3%) produced

was filtered and recrystallised from ethanol to yield colourless prisms of 1-(4-nitrobenzamidomethyl)-cyclohexyldimethylaminehydrochloride, m.p. 271-3° (Found: C,56.22; H,7.03; N,12.29; equiv., 310.1. $C_{16}H_{24}ClN_3O_3$ requires C,56.35; H,7.07; N,12.16%; equiv., 305.0), $\nu_{max.}$(nujol), 3250 (NH), 2700-2600 (NH^+), 1655 (amide CO), 1600, 1550, 1520, 1355, 1140, 880, 720 (Ph)cm^{-1}.

τ (TFA) 8.50 (10H, m, cyclohexyl-CH_2's), 7.40 (6H, m, $(CH_3)_2N^+$), 6.40 (2H, m, NH-CH_2), 2.30 (4H, m, aromatic H's).

1-(2-Methoxybenzamidomethyl)-cyclohexyldimethylamine (59)

A mixture of 1-aminomethylcyclohexyldimethylamine (1.5g), 2-methoxybenzoyl chloride ($3cm^3$) and pyridine ($7cm^3$) was allowed to stand at room temperature for 1hr. The white solid (1.56g, 49.7%) produced was filtered and recrystallised from ethanol to yield colourless prisms of 1-(2-methoxybenzamidomethyl)-cyclohexyldimethylaminehydrochloride, m.p. 199-200° (Found: C,62.47; H,8.27; N,8.58; equiv., 330.1. $C_{17}H_{27}ClN_2O_2$ requires C,62.71; H,8.35; N,8.46%; equiv., 291.0), $\nu_{max.}$(nujol), 3300 (NH), 2650-2550 (NH^+), 1660 (amide CO), 1600, 1550, 1315, 1150, 1020, 770 (Ph)cm^{-1}.

τ (D_2O) 8.30 (10H, m, cyclohexyl-CH_2's), 7.15 (6H, s, $(CH_3)_2N^+$), 6.25 (2H, s, NH-CH_2), 6.15 (3H, s, O-CH_3), 2.60 (4H, m, aromatic H's).

1-(4-Chlorobenzamidomethyl)-cyclohexyldimethylamine (60)

A mixture of 1-aminomethylcyclohexyldimethylamine (1.5g), 4-chlorobenzoyl chloride ($3cm^3$) and pyridine ($7cm^3$) was allowed to stand at room temperature for 1hr. When no crystallisation occurred the mixture was heated on a water-bath for 8hr. The mixture was cooled and the solid (1.8g, 56.6%) was filtered and recrystallised from ethanol to yield colourless prisms of 1-(4-chlorobenzamidomethyl)-

cyclohexyldimethylaminehydrochloride, m.p. 197-8° (Found: C,57.79; H,7.14; N,8.32; Cl,20.89; equiv., 327.5. $C_{16}H_{24}Cl_2N_2O$ requires C,58.01; H,7.25; N,8.46; Cl,21.45%; equiv., 295.5), $\nu_{max.}$(nujol), 3280 (NH), 2650-2500 (NH^+), 1640 (amide CO), 1600, 1560, 1320, 1090, 1020, 980, 930, 840, 740 (Ph)cm^{-1}.

τ(D_2O) 8.30 (10H, m, cyclohexyl-CH_2's), 7.10 (6H, s, $(CH_3)_2N^+$), 6.15 (2H, s, NH-CH_2), 2.45 (4H, d, aromatic H's).

1-(4-Methoxybenzamidomethyl)-cyclohexyldimethylamine (61)

A mixture of 1-aminomethylcyclohexyldimethylamine (1.5g), 4-methoxybenzoyl chloride ($3cm^3$) and pyridine ($7cm^3$) was allowed to stand at room temperature for 1hr. The white solid (2.06g, 65.6%) produced was filtered and recrystallised from ethanol to yield colourless prisms of 1-(4-methoxybenzamidomethyl)-cyclohexyldimethylaminehydrochloride, m.p. 215° (Found: C,62.42; H,8.50; N,8.58; equiv., 312.7. $C_{17}H_{27}ClN_2O_2$ requires C,62.47; H,8.27; N,8.58%; equiv., 291.0), $\nu_{max.}$(nujol), 3310, 3260 (NH), 2700-2500 (NH^+), 1660 (amide CO), 1610, 1545, 1515, 1320, 1255, 1190, 1020, 870, 855, 780 (Ph)cm^{-1}.

τ(D_2O) 8.40 (10H, m, cyclohexyl-CH_2's), 7.20 (6H, s, $(CH_3)_2N^+$), 6.25 (2H, s, NH-CH_2), 6.20 (3H, s, O-CH_3), 3.00 (2H, d, aromatic H's), 2.30 (2H, d, aromatic H's).

1-(2-Naphthamidomethyl)-cyclohexyldimethylamine (62)

A mixture of 1-aminomethylcyclohexyldimethylamine (1.5g), 2-naphthoyl chloride ($2cm^3$) and pyridine ($7cm^3$) was allowed to stand at room temperature for 1hr. The yellow solid (2.84g, 85.2%) produced was filtered and recrystallised from ethanol to yield colourless prisms of 1-(2-naphthamidomethyl)-cyclohexyldimethylaminehydrochloride, m.p. 200° (Found: C,68.98; H,7.60; N,7.84: $C_{20}H_{27}ClN_2O$ requires C,69.26; H,7.79; N,8.08%), $\nu_{max.}$(nujol), 3200 (NH), 2700-2500

(NH^+), 1660 (amide CO), 1600, 1540, 1300, 1280, 1235, 1140, 830, 780, 760, 720 (Ph)cm^{-1}.

τ(D_2O) 8.40 (10H, m, cyclohexyl-CH_2's), 7.25 (6H, s, $(CH_3)_2N^+$), 6.55 (2H, s, NH-CH_2), 2.10 (7H, m, aromatic H's).

1-(4-Bromobenzamidomethyl)-cyclohexyldimethylamine (63)

A mixture of 1-aminomethylcyclohexyldimethylamine (1.5g), 4-bromobenzoyl chloride ($2cm^3$) and pyridine ($7cm^3$) was allowed to stand at room temperature for 1hr. When no crystallisation occurred the mixture was heated on a water-bath for 1hr. The mixture was cooled and the white solid (2.5g, 88.0%) produced was filtered and recrystallised from ethanol to yield colourless prisms of 1-(4-bromobenzamidomethyl)-cyclohexyldimethylaminehydrochloride, m.p. 217° (Found: C,51.22; H,6.50; N,7.37. $C_{16}H_{24}BrClN_2O$ requires C,51.13; H,6.39; N,7.47%), $\nu_{max.}$(nujol), 3250 (NH), 2600-2500 (NH^+), 1660 (amide CO), 1595, 1550, 1295, 1140, 1015, 850, 760 (Ph), 670 (C-Br)cm^{-1}.

τ(D_2O) 8.35 (10H, m, cyclohexyl-CH_2's), 7.15 (6H, s, $(CH_3)_2N^+$), 6.20 (2H, s, NH-CH_2's), 2.40 (4H, s, aromatic H's).

1-(3-Bromobenzamidomethyl)-cyclohexyldimethylamine (64)

A mixture of 1-aminomethylcyclohexyldimethylamine (1.5g), 3-bromobenzoyl chloride ($2cm^3$) and pyridine ($7cm^3$) was allowed to stand at room temperature for 1hr. The white solid (1.5g, 41.5%) produced was filtered and recrystallised from ethanol to yield colourless prisms of 1-(3-bromobenzamidomethyl)-cyclohexyldimethylaminehydrochloride, m.p. 252° (Found: C,51.33; H,6.37; N,7.41. $C_{16}H_{24}BrClN_2O$ requires C,51.13; H,6.39; N,7.46%), $\nu_{max.}$(nujol), 3250 (NH), 2600-2500 (NH^+), 1650 (amide CO), 1550, 1320, 1150, 1025, 760, 720, 690 (Ph)cm^{-1}.

τ(TFA) 8.60 (10H, m, cyclohexyl-CH_2's), 7.50 (6H, s, $(CH_3)_2N^+$), 6.35 (2H, s, NH-$C\underline{H}_2$), 2.60 (4H, m, aromatic H's).

1-(4-Hydroxybenzamidomethyl)-cyclohexyldimethylamine ethoxyformate (65)

A mixture of 1-aminomethylcyclohexyldimethylamine (1.5g), 4-hydroxybenzoyl chloride, ethoxyformic ester ($2cm^3$) and pyridine ($10cm^3$) was allowed to stand at room temperature for 1hr. The white solid (2.0g, 55.1%) produced was filtered and recrystallised from ethanol to yield colourless prisms of 1-(4-hydroxybenzamidomethyl)-cyclohexyldimethylamineethoxyformicesterhydrochloride, m.p. 197° (Found: C,58.98; H,7.49; N,7.07. $C_{19}H_{29}ClN_2O_4$ requires C,59.30; H,7.54; N,7.28%), $\nu_{max.}$(nujol), 3250 (NH), 2700-2500 (NH^+), 1750 (ester CO), 1660 (amide CO), 1600, 1540, 1500, 1450, 1375, 1315, 1285, 1250, 1210, 1170, 1140, 1100, 1060, 1005, 980, 910, 700 (Ph)cm^{-1}.

τ(D_2O) 8.80 (3H, t, $CH_2C\underline{H}_3$), 8.30 (10H, m, cyclohexyl-CH_2's), 7.10 (8H, m, $(CH_3)_2N^+$ and $C\underline{H}_2CH_3$), 6.10 (2H, s, NH-$C\underline{H}_2$), 2.70 (2H, d, aromatic H's), 2.20 (2H, d, aromatic H's).

1-(3,4-Dichlorocinnamamidomethyl)-cyclohexyldimethylamine (66)

A mixture of 1-aminomethylcyclohexyldimethylamine (1.5g), 3,4-dichlorocinnamoyl chloride ($2cm^3$) and pyridine ($10cm^3$) was allowed to stand at room temperature for 1hr. The white solid (1.69g, 34.9%) produced was filtered and recrystallised from ethanol to yield colourless prisms of 1-(3,4-dichlorocinnamamidomethyl)-cyclohexyldimethylaminehydrochloride, m.p.225° (Found: C,55.24; H,6.57; N,7.16. $C_{18}H_{25}Cl_3N_2O$ requires C,55.17; H,6.39; N,7.15%), $\nu_{max.}$(nujol), 3230 (NH), 2650-2500 (NH^+), 1675 (amide CO), 1640 (C=C), 1565, 1220, 1150, 990, 835, 720 (Ph)cm^{-1}.

$\tau(D_2O)$ 8.50 (10H, m, cyclohexyl-CH_2's), 7.30 (6H, s, $(CH_3)_2N^+$), 6.50 (2H, s, NH-$C\underline{H}_2$), 3.20 (1H, d, CH-CO), 3.00 (1H, d, Ph-CH), 2.10 (3H, m, aromatic H's).

1-(4-Dimethylaminobenzamidomethyl)-cyclohexyldimethylamine (120)

A mixture of 1-aminomethylcyclohexyldimethylamine (1.5g), 4-dimethylaminobenzoyl chloride ($2cm^3$) and pyridine ($10cm^3$) was allowed to stand at room temperature for 1hr. Addition of ether produced a fawn solid (2.0g, 55.3%) which was filtered and recrystallised from ethanol to yield colourless prisms of 1-(4-dimethylaminobenzamidomethyl)-cyclohexyldimethylaminedihydrochloride, m.p. 226° (Found: C,47.89; H,8.52. $C_{18}H_{31}Cl_2N_3O$ requires C,48.21; H,8.71%), $\nu_{max.}$(nujol), 3280 (NH), 2700-2500 (NH^+), 1660 (amide CO), 1600, 1520, 1310, 1290, 1215, 850, 780 (Ph)cm^{-1}.

$\tau(D_2O)$ 8.60 (10H, m, cyclohexyl-CH_2's), 7.80 (12H, s, $(CH_3)_2N^+$), 6.40 (2H, s, NH-$C\underline{H}_2$), 2.65 (4H, s, aromatic H's).

1-(4-Ethoxybenzamidomethyl)-cyclohexyldimethylamine (121)

A mixture of 1-aminomethylcyclohexyldimethylamine (1.5g), 4-ethoxybenzoyl chloride ($2cm^3$) and pyridine ($7cm^3$) was allowed to stand at room temperature for 1hr. The white solid (2.4g, 73.3%) produced was filtered and recrystallised from ethanol to yield colourless prisms of 1-(4-ethoxybenzamidomethyl)-cyclohexyldimethylaminehydrochloride, m.p. 206° (Found: C,62.30; H,8.45; N,8.18. $C_{18}H_{29}ClN_2O_2$ requires C,63.44; H,8.52; N,8.22%), $\nu_{max.}$(nujol), 3220 (NH), 2700-2500 (NH^+), 1650 (amide CO), 1600, 1540, 1315, 1250, 1175, 1045, 780, 730 (Ph)cm^{-1}.

$\tau(D_2O)$ 8.45 (3H, t, $CH_2C\underline{H}_3$), 8.25 (10H, m, cyclohexyl-CH_2's), 7.10 (6H, s, $(CH_3)_2N^+$), 6.20 (4H, broad m, O-CH_2 and NH-$C\underline{H}_2$), 2.50 (4H, m, aromatic H's).

1-(4-Toluamidomethyl)-cyclohexyldimethylamine (122)

A mixture of 1-aminomethylcyclohexyldimethylamine (1.5g), 4-toluoyl chloride ($2cm^3$) and pyridine ($10cm^3$) was allowed to stand at room temperature for 1hr. Addition of ether yielded a yellow solid (2.7g, 87.1%) which was filtered and recrystallised from ethanol to yield colourless prisms of 1-(4-toluamidomethyl)-cyclohexyldimethylamine-hydrochloride, m.p. 197° (Found: C,65.47; H,8.53; N,8.82; Cl,11.20. $C_{17}H_{27}ClN_2O$ requires C,65.70; H,8.69; N,9.01; Cl,11.43%), $\nu_{max.}$ (nujol), 3250 (NH), 2600-2500 (NH^+), 1650 (amide CO), 1545, 1300, 1140, 845, 760 (Ph)cm^{-1}.

τ(D_2O) 8.30 (10H, m, cyclohexyl-CH_2's), 7.65 (3H, s, aromatic-CH_3), 7.15 (6H, s, $(CH_3)_2N^+$), 6.20 (2H, s, NH-CH_2), 2.75 (2H, d, aromatic H's), 2.30 (2H, d, aromatic H's).

1-(3,4-Dimethoxybenzamidomethyl)-cyclohexyldimethylamine (123)

A mixture of 1-aminomethylcyclohexyldimethylamine (1.5g), 3,4-dimethoxybenzoyl chloride ($2cm^3$) and pyridine ($10cm^3$) was allowed to stand at room temperature for 1hr. The white solid (1.4g, 40.8%) produced was filtered and recrystallised from ethanol to yield colourless prisms of 1-(3,4-dimethoxybenzamidomethyl)-cyclohexyl-dimethylaminehydrochloride, m.p. 212° (Found: C,60.58; H,8.16; N,7.85. $C_{18}H_{29}ClN_2O_3$ requires C,60.60; H,8.13; N,7.86%), $\nu_{max.}$ (nujol), 3240 (NH), 2650-2500 (NH^+), 1660 (amide CO), 1600, 1500, 1260, 1215, 1120, 750 (Ph)cm^{-1}.

τ(D_2O) 8.25 (10H, m, cyclohexyl-CH_2's), 7.15 (6H, s, $(CH_3)_2N^+$), 6.20 (2H, s, NH-CH_2), 6.15 (6H, s, $(O-CH_3)_2$), 2.85 (1H, s, aromatic H), 2.65 (2H, s, aromatic H's).

B: α-AMINONITRILES, α-AMINOESTERS AND THEIR URETHANS

2-Ethylamino-2-methyl-3-phenylpropanonitrile (84a)

A solution of potassium cyanide (6.8g) and ethylamine hydrochloride (8.15g) in water ($5cm^3$) and a solution of benzylmethylketone (13.4g) in methanol ($2cm^3$) were mixed and stirred at room temperature for 72hr. The mixture was extracted with ether and the ethereal extract dried ($MgSO_4$) and evaporated under reduced pressure to yield a colourless, mobile oil (17.7g, 94.0%), $\nu_{max.}$ (liquid film), 3330 (NH), 2240 (C≡N), 1460, 760, 700 (Ph)cm^{-1}. τ ($CDCl_3$), 8.90 (3H, t, $CH_2\underline{CH}_3$), 8.60 (3H, s, CH_3), 7.90 (1H, s, NH), 7.20 (2H, q, $\underline{CH}_2CH_3$), 7.10 (2H, s, benzyl-CH_2), 2.70 (5H, s, aromatic H's). Treatment of an aliquot with 10% ethanolic hydrochloric acid yielded a solid which recrystallised from ethanol as colourless prisms of 2-ethylamino-2-methyl-3-phenylpropanonitrilehydrochloride, m.p. 135° (Found: C,63.91; H,7.65; N,12.23. $C_{12}H_{17}ClN_2$ requires C,64.15; H,7.57; N,12.47%), $\nu_{max.}$ (nujol), 3350 (NH), 2750-2400 (NH^+), 760, 700 (Ph)cm^{-1}.

Attempted preparation of N-carboethoxy-1-cyano-N-ethyl-1-methyl-2-phenylethylamine

Ethyl chloroformate (1.52g) was added dropwise to a stirred, cooled solution of 2-ethylamino-2-methyl-3-phenylpropanonitrile (5.17g), ether ($25cm^3$) and water ($12.5cm^3$). A further portion of ethyl chloroformate (1.52g) and sodium hydroxide (2.84g) in water ($10cm^3$) were added dropwise simultaneously at the same rate to the mixture. The mixture was stirred at 0° for 0.5hr, the ether layer separated, the aqueous layer extracted with ether and the ethereal solutions bulked, dried ($MgSO_4$) and evaporated under reduced pressure to yield a sticky solid which was triturated with light petroleum (b.p. 60-80°)

to yield a white solid (2-ethylamino-2-methyl-3-phenylpropano-nitrilehydrochloride). The filtrate was evaporated under reduced pressure to yield a yellow, mobile oil which was identical with the original material.

3-(4-Chlorophenyl)-2-ethylamino-2-methylpropanonitrile (84b)

A solution of potassium cyanide (1.63g) and ethylamine hydrochloride (2.04g) in water ($5cm^3$) and a solution of 4-chlorobenzylmethyl-ketone (4.21g) in methanol ($2cm^3$) were mixed and stirred at room temperature for 72hr. The mixture was extracted with ether and the ethereal extract dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow, mobile oil which solidified on standing. The yellow solid (3.83g, 68.9%) was recrystallised from light petroleum (b.p. 60-80°) to yield colourless needles of 3-(4-chlorophenyl)-2-ethylamino-2-methylpropanonitrile, m.p. 54° (Found: C,64.58; H,6.70; N,12.30. $C_{12}H_{15}ClN_2$ requires C,64.72; H,6.74; N,12.58%), $\nu_{max.}$(nujol), 3300 (NH), 2200 (C≡N), 1500, 1410, 1240, 1210, 1150, 1120, 1055, 1020, 855, 815, 780, 720 (Ph)cm^{-1}.

$\tau(CDCl_3)$ 8.90 (3H, t, $CH_2\underline{CH_3}$), 8.60 (3H, s, CH_3), 8.30 (1H, broad s, NH), 7.30 (2H, q, $\underline{CH_2}CH_3$), 7.10 (2H, s, benzyl-CH_2), 2.75 (4H, s, aromatic H's).

Attempted preparation of N-carboethoxy-2-(4-chlorophenyl)-1-cyano-N-ethyl-1-methylethylamine

3-(4-Chlorophenyl)-2-ethylamino-2-methylpropanonitrile (2.25g) was placed into a stirred, cooled (0°) mixture of water ($12.5cm^3$) and ether ($25cm^3$). Ethyl chloroformate (0.7g) was added dropwise. A further portion of ethyl chloroformate (0.7g) and a solution of sodium hydroxide (1.2g) in water ($5cm^3$) were added dropwise simultaneously at the same rate. After the final addition the

mixture was stirred at 0-5° for a further 1.5hr. The ether layer was separated, the aqueous layer extracted with ether, the ether fractions combined, dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow, mobile oil which solidified on standing and was identical with the original material.

2-Amino-2-methyl-3-phenylpropanonitrile (87a)

Potassium cyanide (6.5g) and ammonium chloride (5.35g) were dissolved in the least possible amount of water. Benzylmethylketone (13.4g) was dissolved in the least possible amount of methanol. The two solutions were mixed and stirred at room temperature for 72hr, extracted with ether, the ethereal extract dried ($MgSO_4$) and evaporated under reduced pressure to yield a pale yellow, mobile oil (18.0g, 95.0%) which was shown, by comparison of infrared spectrum and NMR spectrum, to be identical with the compound prepared by the method of Stein, Bronner and Pfister[81], $\nu_{max.}$ (liquid film), 3370 (NH_2), 2200 (C≡N), 1450, 1110, 755, 700 (Ph) cm^{-1}. τ ($CDCl_3$) 8.50 (3H, s, CH_3), 7.65 (2H, broad s, NH_2), 7.10, 6.60 (2H, d and s, CH_2), 2.70 (5H, s, aromatic H's).

2-Carboethoxyamino-2-methyl-3-phenylpropanonitrile (88)

To a stirred, cooled (0°) mixture of ether ($25cm^3$), water ($12.5cm^3$) and 2-amino-2-methyl-3-phenylpropanonitrile (4.4g) was added ethyl chloroformate (1.52g). A further portion of ethyl chloroformate (1.52g) in ether ($10cm^3$) and sodium hydroxide (2.84g) in water ($10cm^3$) were added dropwise simultaneously at the same rate. After 0.5hr the ethereal layer was separated and the aqueous layer extracted with ether. The ethereal extracts were combined, dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow, viscous oil (2.63g, 41.2%) which was distilled *in vacuo* to yield 2-(*N*-carbo-

ethoxyamino-2-methyl-3-phenylpropanonitrile, b.p. 188-92°/4.0mm as a colourless, viscous oil (Found: M^+,232.121170. $C_{13}H_{16}N_2O_2$ requires M^+,232.121145), $\nu_{max.}$(liquid film), 3350 (NH), 2230 (C≡N), 1705 (urethan CO), 1455, 1260, 760, 700 (Ph)cm^{-1}.

2-Amino-3-(4-chlorophenyl)-2-methylpropanonitrile (87b)

Potassium cyanide (1.63g) and ammonium chloride (1.34g) were dissolved in the least possible amount of water. 4-Chlorophenylacetone (4.21g) was dissolved in the least possible amount of methanol. The two solutions were mixed and stirred at room temperature for 72hr, extracted with ether, the ethereal extract dried ($MgSO_4$) and evaporated under reduced pressure to yield a dark, red oil (4.50g, 92.6%), $\nu_{max.}$(liquid film), 3450 (NH_2), 2250 (C≡N), 1500, 1180, 1020, 810 (Ph)cm^{-1}. Although this compound showed the spectral characteristics of the desired compound, distillation in vacuo yielded a yellow, viscous oil, b.p.216-22°/2.5mm, the infrared spectrum of which indicated a loss of hydrogen cyanide by elimination (lack of nitrile peak at 2250cm^{-1} and appearance of a peak at 1660cm^{-1} which is in the correct region for an olefinic double bond).

Attempted preparation of 2-N-carboethoxyamino-3-(4-chlorophenyl)-2-methylpropanonitrile

To a mixture of 2-amino-3-(4-chlorophenyl)-2-methylpropanonitrile (3.9g), ether (25cm^3) and water (12.5cm^3) was added with cooling and stirring ethyl chloroformate (1.52g). A further portion of ethyl chloroformate (1.52g) and a solution of sodium hydroxide (2.84g) in water (10cm^3) were added dropwise simultaneously at the same rate. 0.5hr after the final addition the mixture was extracted with ether, the ethereal extract dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow oil which was shown to be identical with

the original material.

Attempts to prepare 3-cyano-3-methyl-1-oxo-1,2,3,4-tetrahydro-isoquinoline

(1). 2-Carboethoxyamino-2-methyl-3-phenylpropanonitrile (1.25g) was dissolved in chloroform ($20cm^3$) and phosphorus oxychloride (1.5g) added. The mixture was heated on a water-bath for 4hr, poured carefully into hot water and allowed to cool. The solution was made alkaline using 10% sodium hydroxide solution, extracted with chloroform, the chloroform extract dried ($MgSO_4$) and evaporated under reduced pressure to yield a brown, mobile oil which was identical with the original material.

(2). 2-Carboethoxyamino-2-methyl-3-phenylpropanonitrile (2.0g) was heated at 105^o with phosphorus oxychloride ($15cm^3$) for 4hr, poured onto ice and extracted with ether. The aqueous portion was made alkaline using 10% sodium hydroxide solution, extracted with chloroform, the chloroform extract dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow, mobile oil which was identical with the original material.

(3). 2-Carboethoxyamino-2-methyl-3-phenylpropanonitrile (2.0g) was heated at 105^o with polyphosphoric ester ($15cm^3$) for 2hr, poured onto ice and extracted with ether. The aqueous portion was made alkaline using 10% sodium hydroxide solution, extracted with chloroform, the chloroform extract dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow, mobile oil which was identical with the original material.

2-(N-carboethoxyamino)-2-methyl-3-phenylpropanoic acid ethyl ester (90a)

To a stirred, cooled mixture of ether ($25cm^3$), water ($12.5cm^3$) and

2-amino-2-methyl-3-phenylpropanoic acid ethyl ester (2.07g) was added ethyl chloroformate (1.08g). A further portion of ethyl chloroformate (1.08g) in ether ($10cm^3$) and sodium hydroxide (1.47g) in water ($10cm^3$) were added dropwise simultaneously at the same rate. After 0.5hr the ethereal layer was separated and the aqueous layer extracted with ether. The ethereal extracts were combined, dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow, viscous oil (2.0g, 71.7%) which was distilled in vacuo to yield 2-(N-carboethoxyamino)-2-methyl-3-phenylpropanoicacidethylester, b.p. 150-4°/2.5mm, as a colourless, viscous oil (Found: C,64.46; H,7.49; N,5.20. $C_{15}H_{21}NO_4$ requires C,64.52; H,7.53; N,5.02%), $\nu_{max.}$ (liquid film), 3400 (NH), 1740 (broad-ester and urethan CO's), 1500, 1450, 1370, 1260, 1200, 1090, 1050, 1040, 670 (Ph)cm^{-1}.

Attempts to prepare 3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ethyl ester

(1). 2-Carboethoxyamino-2-methyl-3-phenylpropanoic acid ethyl ester (2.0g) was dissolved in chloroform ($20cm^3$) and phosphorus oxychloride (2.0g) was added. The mixture was heated on a steam-bath for 4hr, poured carefully onto hot water and allowed to cool. The solution was made alkaline using 10% sodium hydroxide solution, extracted with chloroform, the chloroform extract dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow, mobile oil which was identical with the original material.

(2). 2-Carboethoxyamino-2-methyl-3-phenylpropanoic acid ethyl ester (2.0g) was heated at 105° in phosphorus oxychloride ($20cm^3$) for 4hr, poured onto ice and extracted with ether. The aqueous portion was made alkaline using 10% sodium hydroxide solution and worked up as in (1) to yield a yellow, mobile oil which was identical with the original material.

(3). 2-Carboethoxyamino-2-methyl-3-phenylpropanoic acid ethyl ester (2.0g) was heated at 105° with polyphosphoric ester ($20cm^3$) for 4hr, poured carefully onto ice and extracted with ether. The aqueous portion was made alkaline using 10% sodium hydroxide solution and worked up as in (1) to yield a yellow, mobile oil which was identical with the original material.

2-Carboethoxyamino-3-(3,4-dimethoxyphenyl)-2-methylpropanoic acid ethyl ester (90b)

To a stirred, cooled (0°) mixture of ether ($25cm^3$), water ($12.5cm^3$) and 2-amino-3-(3,4-dimethoxyphenyl)-2-methylpropanoic acid ethyl ester (2.67g) was added ethyl chloroformate (1.08g). A further portion of ethyl chloroformate (1.08g) in ether ($10cm^3$) and sodium hydroxide (1.47g) in water ($10cm^3$) were added dropwise, simultaneously, at the same rate. After 0.5hr the ethereal layer was separated and the aqueous layer extracted with ether. The ethereal extracts were combined, dried ($MgSO_4$) and evaporated under reduced pressure to yield white microprisms (1.50g, 44.3%) of 2-carboethoxyamino-3-(3,4-dimethoxyphenyl)-2-methylpropanoic-acidethylester, m.p. 188° (Found: M^+, 339.168175. $C_{17}H_{25}NO_6$ requires M^+, 339.168318), $\nu_{max.}$(nujol), 3400 (NH), 1720 (broad-contains ester and urethan CO's), 1520, 1330, 1305, 1270, 1240, 1160, 1145, 1120, 1075, 1035, $690cm^{-1}$.

τ($CDCl_3$) 8.80 (9H, m, 2 x $CH_2\underline{CH}_3$'s and CH_3), 8.40 (2H, s, benzyl-CH_2), 6.65 (2H, q, urethan $\underline{CH}_2CH_3$), 6.20 (6H, s, OCH_3's), 5.85 (2H, q, ester $\underline{CH}_2CH_3$), 4.60 (1H, s, NH), 3.35 (2H, d, 2',3' aromatic H's), 2.60 (1H, s, 5' aromatic H).

6,7-Dimethoxy-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ethyl ester (94)

2-Carboethoxyamino-3-(3,4-dimethoxyphenyl)-2-methylpropanoic acid ethyl ester (1.5g) was heated at 105° with phosphorus oxychloride (20cm^3) for 2hr, poured onto ice and extracted with ether. The aqueous portion was made alkaline using 10% sodium hydroxide solution, extracted with chloroform, the chloroform extract dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow, mobile oil which, on trituration with ether, yielded a white solid (0.15g, 11.7%) which was recrystallised from acetone/light petroleum (b.p.60-80°) to yield colourless prisms of 6,7-dimethoxy-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylicacidethyl-ester, m.p. 161° (Found: C,61.20; H,6.80; N,4.54. $C_{15}H_{19}NO_5$ requires C,61.43; H,6.48; N,4.78%), $\nu_{max.}$(nujol), 3250 (NH), 3120 (NH), 1725 (ester CO), 1670 (amide CO), 1600, 1530, 1440, 1390, 1280, 1225, 1200, 1115, 1090cm^{-1}.

τ($CDCl_3$) 8.80 (3H, t, $CH_2\underline{CH}_3$), 8.50 (3H, s, CH_3), 8.20 (2H, s, ring CH_2), 6.10 (6H, s, OCH_3's), 5.85 (2H, q, $C\underline{H}_2CH_3$), 3.30 (1H, s, NH), 2.65 (1H, s, C(5)-H), 2.40 (1H, s, C(8)-H).

Attempted preparation of N-carboethoxy-1-cyano-2-(3,4-dimethoxyphenyl)-1-methylethylamine

Ethyl chloroformate (1.91g) was added dropwise to a stirred, cooled (0°) mixture of 2-amino-3-(3,4-dimethoxyphenyl)-2-methylpropanonitrile (4.0g), ether (25cm^3) and water (12.5cm^3). A further portion of ethyl chloroformate (1.91g) and sodium hydroxide (2.64g) in water (10cm^3) were added dropwise, simultaneously, at the same rate. The mixture was stirred at 0° for 0.5hr, the ether layer separated, the aqueous layer extracted with ether and the ethereal solutions bulked, dried ($MgSO_4$) and evaporated under reduced

pressure to yield a red, mobile oil which was identical with the original material.

Attempted preparation of 6,7-dimethoxy-3-(1-hydroxy-1-methylethyl)-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline

Magnesium turnings (0.24g) were added to dry ether ($20cm^3$), containing one crystal of iodine. Approximately one third of a solution of methyl iodide (1.41g) in dry ether ($20cm^3$) was added. Once reaction had commenced, the remainder of the methyl iodide solution was added dropwise at a rate sufficient to keep the mixture refluxing gently. 6,7-Dimethoxy-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ethyl ester (1.48g) was added in several portions. The reaction mixture was stirred for 10min after the final addition and heated on a water-bath for 15min to complete any reaction. Excess Grignard reagent was destroyed by the dropwise addition of dilute ammonium chloride solution. The ether solution was separated, filtered, dried ($MgSO_4$) and evaporated under reduced pressure to yield 1.4g of a white solid which was shown by m.p. and infrared spectrum to be identical with the starting material.

C: INDANONES

3-Diethylamino-2-methyl-1-indanone (101)

2-Bromo-2-methyl-1-indanone (23.0g) in ethanol (307cm^3) was treated dropwise with a solution of diethylamine (37.3g) in ethanol (15cm^3), the mixture refluxed for 4hr and the ethanol removed under reduced pressure. The residue was partitioned between dilute hydrochloric acid and ether, the acidic portion made alkaline using 10% sodium hydroxide solution, extracted with ether, the ethereal extract dried ($MgSO_4$) and evaporated under reduced pressure to yield a dark, brown, mobile oil. The oil was neutralised using 10% ethanolic hydrochloric acid and the solution was evaporated under reduced pressure to yield a dark, brown oil which was dissolved in iso-propanol, decolourised with charcoal and stood at 0° overnight. A small amount of ether was added to the solution and, on standing overnight at 0° and scratching, a white solid (1.93g, 7.50%) was produced which was recrystallised from ethanol/ether to yield colourless prisms of 3-diethylamino-2-methyl-1-indanonehydrochloride, m.p. 142° (Found: C,65.99; H,7.72; N,5.64. $C_{14}H_{20}ClNO$ requires C,66.27; H,7.89; N,5.52%), $\nu_{max.}$(nujol), 2600-2500 (NH^+), 1720 (CO), 745cm^{-1}.

τ (D_2O), 8.60 (3H, s, CH_3), 8.45 (6H, t, ethyl CH_3's), 6.80 (5H, m, C-2 H and ethyl CH_2's), 5.05 (1H, s, C-3 H), 2.30 (4H, m, aromatic H's).

2-Dimethylaminomethyl-2-methyl-1-indanone (107a)

2-Methyl-1-indanone (2.92g), dimethylaminehydrochloride (1.8g) and 40% formalin solution (1.5cm^3) were refluxed for 0.5hr, cooled and evaporated to dryness under reduced pressure to yield a yellow, viscous oil. Trituration of this oil with light petroleum (b.p. 60-80°)/acetone yielded a yellow solid (4.0g, 83.5%) which was

recrystallised from acetone/methanol to yield colourless prisms of 2-dimethylaminomethyl-2-methyl-1-indanonehydrochloride, m.p.115°, $\nu_{max.}$(nujol), 2600-2500 (NH^+), 1710 (CO), 1610, 1420, 1290, 970, 740, 715cm^{-1}.

τ(D_2O), 8.74 (3H, s, CH_3), 7.30 (2H, s, N-CH_2), 7.15 (6H, s, N-CH_3's), 6.75 (1H, m, C-3 H), 6.50 (1H, s, C-3 H), 2.35 (4H, m, aromatic H's). Several attempts at analysis were unsuccessful due to the hygroscopic nature of the compound.

2-Diethylaminomethyl-2-methyl-1-indanone (107b)

2-Methyl-1-indanone (2.92g), diethylaminehydrochloride (2.42g) and 40% formalin solution (1.5cm^3) were refluxed for 0.5hr, cooled and evaporated to dryness under reduced pressure to yield a yellow, mobile oil. Trituration of this oil with light petroleum (b.p. 60-80°)/acetone yielded a white solid which was filtered off and found to be diethylaminehydrochloride. The filtrate was evaporated to dryness under reduced pressure and the resultant oil triturated with ethyl acetate/ether to yield a white solid (1.6g, 18.9%) which was recrystallised from acetone/methanol to yield colourless prisms of 2-diethylaminomethyl-2-methyl-1-indanonehydrochloride, m.p. 128° (partially melts, then resolidifies and melts at 226°), (Found: M^+, 231.162306. $C_{15}H_{21}N_2O$ requires M^+, 231.162093), $\nu_{max.}$(nujol), 2670-2500 (NH^+), 1710 (CO), 1610, 1400, 1295, 1230, 1200, 970, 735cm^{-1}.

τ(D_2O), 8.77 (3H, s, CH_3), 8.70 (6H, t, ethyl CH_3's), 6.85 (6H, m, N-CH_2 and ethyl CH_2's), 6.55 (2H, d, C-3 H's), 2.40 (4H, m, aromatic H's).

2-Methyl-2-piperidinomethyl-1-indanone (107c)

2-Methyl-1-indanone (2.92g), piperidine (1.88g), 40% formalin

solution (1.5cm^3) and concentrated hydrochloric acid (1cm^3) were refluxed for 0.5hr and evaporated to dryness under reduced pressure. The residue was partitioned between water and ether, the aqueous portion made alkaline using 10% sodium hydroxide solution and extracted with ether. The ethereal extract was dried ($MgSO_4$) and evaporated under reduced pressure to yield a dark, red, mobile oil. This oil was treated with 10% ethanolic hydrochloric acid, evaporated to dryness and triturated with ethyl acetate to yield a yellow solid (1.1g, 19.5%) which was recrystallised from acetone/light petroleum (b.p. 60-80°) to yield colourless prisms of 2-methyl-2-piperidinomethyl-1-indanonehydrochloride, m.p. 152° (Found: C,68.85; H, 7.76; N,5.05. $C_{16}H_{22}ClNO$ requires C,68.69; H,7.87; N,5.01%), $\nu_{max.}$(nujol), 2650-2500 (NH^+), 1700 (CO), 1610, 1420, 1285, 1230, 1205, 1090, 990, 970, 740cm^{-1}.

2-Methyl-2-morpholinomethyl-1-indanone (107d)

2-Methyl-1-indanone (2.92g), morpholine (1.92g), 40% formalin solution (1.5cm^3) and concentrated hydrochloric acid (1cm^3) were refluxed for 0.5hr, cooled and evaporated to dryness under reduced pressure to yield a dark, brown, mobile oil. The oil was dissolved in ethanol and decolourised by refluxing with charcoal for 3hr. The ethanol was removed under reduced pressure and the residue partitioned between water and ether. The aqueous portion was made alkaline using 10% sodium hydroxide solution and extracted with ether. The ethereal extract was dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow, mobile oil. The oil was treated with 10% ethanolic hydrochloric acid, evaporated to dryness under reduced pressure and triturated with ether/ethyl acetate to yield a white solid (1.0g, 17.8%) which was recrystallised from acetone/methanol to yield colourless prisms of 2-methyl-2-morpholinomethyl-

1-indanonehydrochloride, m.p. 145° (Found: C,63.52; H,7.19; N,5.20; M^+, 245.141570. $C_{15}H_{19}NO_2$ requires C,63.94; H,7.10; N,4.97%, M^+, 245.141874), $\nu_{max.}$ (nujol), 2650-2500 (NH^+), 1700 (CO), 1420, 1265, 1220, 1115, 1090, 1065, 975, 870, 705cm^{-1}.

2-Methyl-2-N^4-methylpiperazinomethyl-1-indanone (107e)

2-Methyl-1-indanone (2.92g), N-methylpiperazine (2.2g), 40% formalin solution (1.5cm^3) and concentrated hydrochloric acid (2cm^3) were refluxed for 0.5hr. The mixture was evaporated to dryness under reduced pressure and the residue recrystallised from methanol/acetone to yield N-methylpiperazine hydrochloride. The filtrate was evaporated to dryness and triturated with ethanol/ethyl acetate to yield an off-white solid (3.7g, 62.8%) which was recrystallised from acetone/light petroleum (b.p. 60-80°) to yield colourless prisms of 2-methyl-2-N^4-methylpiperazinomethyl-1-indanonedihydrochloride, m.p. 160° (Found: C,57.55; H,7.19; N,8.36. $C_{16}H_{24}Cl_2N_2O$ requires C,58.01; H,7.25; N,8.46%), $\nu_{max.}$ (nujol), 2700-2400 (NH^+), 1700 (CO), 1605, 1320, 1140, 1070, 1020, 970, 900cm^{-1}.

2-N^4-Methylpiperazinomethyl-1-indanone (106e)

1-Indanone (3.0g), N-methylpiperazine (2.5g), paraformaldehyde (0.7g), ethanol (5cm^3) and concentrated hydrochloric acid (2cm^3) were refluxed for 2hr. The reaction mixture was evaporated to dryness under reduced pressure to yield a dark red oil which was recrystallised from ethanol/ether to yield a yellowish-white solid (3.44g, 47.8%), m.p. 183°(d), $\nu_{max.}$ (nujol), 2700-2450 (NH^+), 1700 (CO), 1280, 1180, 980cm^{-1}. From the infrared spectrum it would appear that this is the desired compound although attempts to obtain correct analysis figures were unsuccessful.

D: ISOQUINOLONES

3-Methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl ester (95)

2-Methyl-1-indanone-2-carboxylic acid methyl ester (3.22g) was added in several portions over 2hr to sodium azide (0.8g) in concentrated sulphuric acid (16.6cm^3) stirred at 0°. The mixture was stirred for 1hr at room temperature, poured onto ice and filtered. The filtrate was made alkaline using 20% sodium carbonate solution and the precipitate filtered and recrystallised from acetone/light petroleum (b.p. 60-80°) to yield fawn needles (0.04g, 1.2%) of 3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acidmethylester, m.p. 152° (Found: C,63.44; H,5.99; N,6.24; M^+, 219.089537. $C_{12}H_{13}NO_3$ requires C,63.16; H,6.14; N,6.14%, M^+, 219.088324), $\nu_{max.}$(nujol), 3200 (NH), 1725 (ester CO), 1660 (amide CO), 1400, 1230, 1120, 755cm^{-1}.

$\tau(CDCl_3)$ 8.40 (2H, s, CH_2), 7.83 (3H, s, CH_3), 6.80 (1H, s, NH), 6.30 (3H, s, OCH_3), 2.60 (4H, m, aromatic H's).

4-Dimethylamino-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline (104b)

3-Dimethylamino-2-methyl-1-indanone hydrochloride (1.0g) was added over 2.5hr to sodium azide (0.2g) in concentrated sulphuric acid (6cm^3) stirred at 0°. The reaction mixture was stirred at room temperature for 1hr, poured onto ice, neutralised with 20% sodium carbonate solution and extracted with ethyl acetate. The ethyl acetate extract was dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow, viscous oil (0.3g, 33.2%) which solidified, on standing at -10°, to yield yellow prisms of 4-dimethylamino-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline, m.p. 142° (Found: C,70.36; H,7.84; N,13.55; M^+, 204.126256. $C_{12}H_{16}N_2O$ requires C,70.59; H,7.84; N,13.76%, M^+, 204.125710),

$\nu_{max.}$(nujol), 3170 (NH), 1650 (CO), 1600, 1160, 1125, 1025, 780, 705cm^{-1}.

4-Diethylamino-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline (104a)

3-Diethylamino-2-methyl-1-indanone hydrochloride (1.5g) was added over 2.5hr to sodium azide (0.3g) in concentrated sulphuric acid (6.5cm^3) stirred at 0°. The reaction mixture was stirred at room temperature for 1hr, poured onto ice, neutralised using 20% sodium carbonate solution and extracted with ethyl acetate. The ethyl acetate extract was dried ($MgSO_4$) and evaporated under reduced pressure to yield a pale, yellow, mobile oil (1.02g, 75.6%). This oil was distilled *in vacuo* (250-5°/7mm) to yield a colourless oil which solidified to yield fawn microprisms of 4-diethylamino-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline, m.p. 234° (Found: M^+, 232.157555. $C_{14}H_{20}N_2O$ requires M^+, 232.158103), $\nu_{max.}$(nujol), 3150 (NH), 1655 (CO), 1570, 1430, 1300, 755cm^{-1}.

2-Oxo-1,2,3,4-tetrahydroquinoline-3-carboxylic acid methyl ester (116)

Sodium azide (0.65g) was added to concentrated sulphuric acid (15cm^3) cooled at 0°. 1-Indanone-2-carboxylic acid methyl ester (1.9g) was added, with stirring, over 2hr. The mixture was stirred at room temperature overnight, poured onto ice and neutralised using 10% sodium carbonate solution. The mixture was extracted with ethyl acetate, dried ($MgSO_4$) and evaporated under reduced pressure to yield a brown, mobile oil which, on trituration with ether, yielded a fawn solid (0.64g, 29.2%), the m.p. and ultraviolet spectrum of which were in agreement with those of an authentic sample of 2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylic acid methyl ester.

3-Dimethylaminomethyl-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline

(109a)

2-Dimethylaminomethyl-2-methyl-1-indanone hydrochloride (2.0g) was added over 2.5hr to sodium azide (0.4g) in concentrated sulphuric acid ($12cm^3$) stirred at 0°. The reaction mixture was stirred at room temperature overnight, poured onto ice, neutralised with 20% sodium carbonate solution and extracted with ethyl acetate. The ethyl acetate extract was dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow, mobile oil (1.6g, 87.9%) which was distilled *in vacuo* to yield a colourless, viscous oil which solidified to yield white prisms of 3-dimethylaminomethyl-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline, m.p. 128° (Found: C,71.20; H,8.02; N,12.59; M^+, 218.141905. $C_{13}H_{18}N_2O$ requires C,71.56; H,8.26; N,12.84%, M^+, 218.142281), $\nu_{max.}$(nujol), 3200 (NH), 1655 (CO), 1600, 1150, 1125, 1100, 1040, 800cm^{-1}.

3-Diethylaminomethyl-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline

(109b)

2-Diethylaminomethyl-2-methyl-1-indanone hydrochloride (1.5g) was added over 2hr to sodium azide (0.4g) in concentrated sulphuric acid ($12cm^3$) stirred at 0°. The reaction mixture was stirred at room temperature for 72hr, poured onto ice, neutralised with 20% sodium carbonate solution and extracted with ethyl acetate. The ethyl acetate extract was dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow, viscous oil which, on standing at -10°, solidified to yield colourless prisms (0.03g, 2.2%) of 3-diethylaminomethyl-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline, m.p. 82° (Found: C,72.94; H,8.96; N,11.14. $C_{15}H_{22}N_2O$ requires C, 73.17; H,8.94; N,11.38%), $\nu_{max.}$(nujol), 3200 (NH), 1655 (CO), 1600, 1575, 1400, 1200, 1150, 1140, 1060, 790, 745, 730cm^{-1}.

3-Methyl-1-oxo-3-piperidinomethyl-1,2,3,4-tetrahydroisoquinoline

(109c)

2-Methyl-2-piperidinomethyl-1-indanone hydrochloride (2.0g) was added to concentrated sulphuric acid ($8cm^3$) stirred at 0^o. Sodium azide (0.63g) was added portionwise over 2hr, the mixture stirred a further 0.5hr at 0^o then overnight at room temperature. The mixture was poured onto ice, made alkaline using 20% sodium carbonate solution, extracted with ethyl acetate, the ethyl acetate extract dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow, viscous oil which, on trituration, yielded a fawn solid (0.33g, 18.1%) which was recrystallised from acetone/light petroleum (b.p. $60-80^o$) to yield colourless prisms of 3-methyl-1-oxo-3-piperidinomethyl-1,2,3,4-tetrahydroisoquinoline, m.p. 120^o (Found: C,74.45; H,8.47; N, 10.87. $C_{16}H_{22}N_2O$ requires C,74.42; H,8.53; N, 10.85%), $\nu_{max.}$(nujol), 3200 (NH), 1650 (CO), 1600, 1160, 1105, 795, 750, 735cm^{-1}.

3-Methyl-3-morpholinomethyl-1-oxo-1,2,3,4-tetrahydroisoquinoline

(109d)

2-Methyl-2-morpholinomethyl-1-indanone hydrochloride (1.0g) was added over 2hr to sodium azide (0.3g) in concentrated sulphuric acid ($9cm^3$) stirred at 0^o. The reaction mixture was stirred overnight at room temperature, poured onto ice, neutralised with 20% sodium carbonate solution and extracted with ethyl acetate. The ethyl acetate solution was dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow, viscous oil (0.55g, 59.6%). The oil, on standing at -10^o, solidified to yield a white solid which was recrystallised from acetone/light petroleum (b.p. $60-80^o$) to yield colourless prisms of 3-methyl-3-morpholinomethyl-1-oxo-1,2,3,4-tetrahydroisoquinoline, m.p. 138^o (Found: C,67.27; H,7.15;

N, 10.22; M^+, 260.152469. $C_{15}H_{20}N_2O_2 \cdot \frac{1}{2}H_2O$ requires C,66.91; H, 7.18; N,10.41%, M^+, 260.153221), $\nu_{max.}$ (nujol), 3350, 3200 (NH), 1650 (CO), 1600, 1400, 1110, 865cm^{-1}.

3-Methyl-3-N^4-methylpiperazinomethyl-1-oxo-1,2,3,4-tetrahydroisoquinoline (109e)

2-Methyl-2-N^4-methylpiperazinomethyl-1-indanone hydrochloride (2.0g) was added to concentrated sulphuric acid (8cm^3) cooled at 0°. Sodium azide (0.63g) was added to the stirred, cooled mixture during 2hr. The mixture was stirred overnight at room temperature, poured onto ice and neutralised using solid sodium carbonate. The mixture was extracted with ethyl acetate, the extract dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow, mobile oil which was stored at -10° for 2 weeks during which time it yielded a fawn solid (0.13g, 7.9%) which was recrystallised from acetone to yield colourless prisms of 3-methyl-3-N^4-methylpiperazinomethyl-1-oxo-1,2,3,4-tetrahydroisoquinoline, m.p. 99° (Found: C,70.43; H,8.33; N,15.44. $C_{16}H_{23}N_3O$ requires C,70.33; H,8.42; N,15.38%), $\nu_{max.}$ (nujol), 3300, 3170 (NH), 1655 (CO), 1160cm^{-1}.

3-Morpholinomethyl-1-oxo-1,2,3,4-tetrahydroisoquinoline (108d)

2-Morpholinomethyl-1-indanone hydrochloride (2.0g) was added to concentrated sulphuric acid (8cm^3) stirred at 0°. Sodium azide (0.63g) was added portionwise over 2hr. The mixture was stirred a further 0.5hr at 0° then overnight at room temperature. The mixture was poured onto ice, made alkaline using 20% sodium carbonate solution, extracted with ethyl acetate, the ethyl acetate extract dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellowish-white solid (1.5g, 81.6%) which was recrystallised from acetone/light petroleum (b.p. 60-80°) to yield straw needles of

3-morpholinomethyl-1-oxo-1,2,3,4-tetrahydroisoquinoline, m.p. 121° (Found: C,68.31; H,7.23; N,11.27. $C_{14}H_{18}N_2O_2$ requires C,68.29; H,7.32; N,11.38%), $\nu_{max.}$(nujol), 3170 (NH), 1650 (CO), 1335, 1300, 1270, 1140, 1105, 870, 740cm^{-1}.

3-N^4-Methylpiperazinomethyl-1-oxo-1,2,3,4-tetrahydroisoquinoline

(108e)

2-N^4-Methylpiperazinomethyl-1-indanone hydrochloride (2.0g) was added to concentrated sulphuric acid (8cm^3) stirred at 0°. Sodium azide (0.63g) was added portionwise over 2hr. The mixture was stirred a further 0.5hr at 0° then overnight at room temperature. The mixture was poured onto ice, made alkaline using 20% sodium carbonate solution, extracted with ethyl acetate, the ethyl acetate extract dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellowish-brown, viscous oil which, on standing, gave a yellowish-white solid (1.5g, 81.3%) which was recrystallised from acetone to yield fawn microprisms of 3-N^4-methylpiperazinomethyl-1-oxo-1,2,3,4-tetrahydroisoquinoline, m.p. 82° (Found: C,69.33; H, 8.26; N,16.20. $C_{15}H_{21}N_3O$ requires C,69.50; H,8.11; N,16.22%), $\nu_{max.}$(nujol), 3400 (NH), 3230 (NH), 1670 (CO), 1610, 1300, 1285, 1240, 1165, 1045, 1015, 815, 750, 700cm^{-1}.

E: PHYSICAL EXPERIMENTAL METHODS

Determination of pKa values.

The method adopted was a modification of that used by Albert and Serjeant[73]. The apparatus was set up and standardised using the buffers stated in the method of Albert and Serjeant. An accurately weighed amount of the base was dissolved in a mixture of methanol and water (50:50). Although this method has been criticised, it is said that the comparison of the basic strengths of a series of substances in a mixed solvent system is valid if the substances are chemically related. Since this was the case in this series of benzamides and bearing in mind the very low water solubility of the bases, it was decided to use a 50% aqueous methanol solution. The initial pH of the solution was noted. The solution was then titrated against N/100 hydrochloric acid. The pH was noted after the addition of each 1.0cm^3 of N/100 hydrochloric acid. Five of these readings were used to calculate the pKa of the compound under test, in a manner analogous to the method of Albert and Serjeant. An example of the calculation is shown below.

Determination of pKa of compound (53).

Weight of compound = 0.019g

Molecular weight of (53) = 260 $\equiv$ 1 litre N HCl

$\equiv$ 100 litres N/100 HCl

Volume of N/100 HCl needed to neutralise 0.019g of (53)

$$= \frac{100,000 \times 0.019}{260} \text{ cm}^3 = 7.31 \text{ cm}^3$$

1 TITRANT N/100 HCl	2 pH	3 STOICHIOMETRIC CONCS. BH^+	4 B	5 BH^+ / B	6 LOG OF COLUMN 5	7 pKa = pH + 6
0.00	9.58	0.000000	0.000073	-	-	-
1.00	9.20	0.000009	0.000064	0.146	-0.85	8.35
2.00	8.90	0.000019	0.000054	0.377	-0.47	8.43
3.00	8.55	0.000029	0.000044	0.659	-0.18	8.37
4.00	8.07	0.000039	0.000034	1.147	+0.06	8.13
5.00	7.28	0.000049	0.000024	2.042	+0.31	7.59

Disregarding the two extreme values this gives a value for the pKa of compound (53) of 8.28($\pm$ 0.15).

Measurement of infrared carbonyl stretching frequencies of substituted benzamidomethylcyclohexyldimethylamines.

The compounds were examined as their solid hydrochlorides and their spectra were recorded as nujol mulls against a reference of air, using a Grubb-Parsons Spectromaster spectrophotometer. The region of the spectrum in which the carbonyl stretching signal occurred (5.5-6.5μ) was examined using a scanning speed of 1μ/4 minutes. The wave-length of the maximum absorption was measured and the value converted from microns to wavenumbers. The results obtained can be seen in Table 4 in Section IIB.

GLC Examination of isomers produced by reaction of 2-bromo-2-methyl-1-indanone with diethylamine.

2-Bromo-2-methyl-1-indanone (2.88g) was stirred for 24hr with diethylamine (4.67g) at room temperature. The reaction mixture was evaporated to dryness and partitioned between dilute hydrochloric acid and ether. The acid layer was basified using 10% sodium

hydroxide solution and extracted with ether. The ethereal solution was separated, dried ($MgSO_4$) and evaporated to yield an oil. $0.1cm^3$ of this oil was diluted to $10cm^3$ with chloroform. 1μLitre of this solution was injected onto a gas-liquid chromatograph under the following conditions:

GLC instrument used: Perkin-Elmer F11 chromatograph.

column used: OV 17 (5%).

pressure of air: 17 lbs/in^2

pressure of hydrogen: 17 lbs/in^2

pressure of nitrogen: 25 lbs/in^2

oven temperature: 170^o

amplification: 20

chart speed: 1cm/min.

The chromatogram obtained is reproduced in Figure 1 in Section IID.

Method for determination of ratio of isomeric bases produced in the reaction of 2-bromo-2-methyl-1-indanone with diethylamine.

The reaction was carried out under various reaction conditions (see Section IID) using a standard amount of 2-bromo-2-methyl-1-indanone whenever appropriate. When the reaction had been completed, the reaction mixture was evaporated to dryness and partitioned between dilute hydrochloric acid and ether. The acid layer was separated, basified using 10% sodium hydroxide solution and extracted with ether. The ethereal solution was dried ($MgSO_4$) and evaporated to yield an oil which was the mixture of bases. $0.1cm^3$ of this mixture was accurately measured and diluted to $10cm^3$ using chloroform. This solution then contained 0.092g of the isomeric mixture. The infrared spectrum of an aliquot of this solution was measured against a reference sample of chloroform using a Grubb-Parsons

Spectromaster spectrophotometer. The region of the spectrum where the carbonyl peaks of the two isomers occurred (5.5-6.5μ) was examined using a scanning speed of 1μ/4 minutes. The ratio of the intensities of the two carbonyl peaks was then measured. The results obtained can be seen in Table 8 in Section IID.

F: MASS SPECTRAL DATA

1-(2-Chlorobenzamidomethyl)-cyclohexyldimethylamine (56)

m/e (I%) 151 (3) 141 (2) 139 (7) 127 (10) 126 (100) 125 (2) 124 (3)
119 (3) 115 (2) 112 (2) 111 (3) 110 (3) 109 (2) 107 (2)
105 (4) 98 (4) 97 (3) 96 (4) 95 (4) 94 (3) 93 (3) 91 (4)
87 (2) 85 (2) 84 (5) 83 (4) 82 (4) 81 (6) 79 (4) 78 (2)
77 (5) 75 (3) 74 (2) 73 (8) 71 (4) 70 (5) 69 (7) 68 (5)
67 (5) 64 (8) 60 (11) 59 (2) 58 (6) 57 (6) 56 (5) 55 (12)
54 (3) 53 (3) 51 (3) 46 (3) 45 (5) 44 (57) 43 (8) 42 (7)
41 (14) 40 (2) 39 (7) 38 (7) 36 (21) 32 (14) 31 (6) 30 (3)
29 (7) 28 (71) 27 (8).

1-(3,4,5-Trimethoxybenzamidomethyl)-cyclohexyldimethylamine (124)

m/e (I%) 212 (9) 197 (3) 164 (1) 127 (9) 126 (100) 125 (1) 124 (1)
110 (2) 96 (2) 84 (4) 82 (2) 81 (3) 70 (2) 68 (2) 67 (1)
58 (5) 56 (2) 55 (4) 54 (1) 53 (2) 46 (2) 44 (1) 42 (5)
41 (4) 36 (1) 32 (3) 30 (6) 29 (2) 28 (16) 27 (2).

m* 183, 77, 52.

1-Cinnamamidomethyl-cyclohexyldimethylamine (57)

m/e (I%) 131 (3) 127 (9) 126 (100) 103 (3) 84 (1) 77 (2) 58 (1)
55 (2) 44 (2) 42 (1) 41 (1) 38 (2) 36 (5) 32 (1) 28 (7).

1-(4-Nitrobenzamidomethyl)-cyclohexyldimethylamine (58)

m/e (I%) 167 (2) 150 (2) 127 (10) 126 (100) 121 (1) 112 (1) 104 (2)
96 (1) 84 (1) 76 (2) 70 (1) 65 (2) 58 (1) 55 (2) 50 (1)
46 (1) 45 (2) 44 (4) 42 (2) 41 (2) 39 (1) 38 (2) 36 (6)
31 (2) 28 (1).

m* 96, 56.5, 52.

1-(2-Methoxybenzamidomethyl)-cyclohexyldimethylamine (59)

m/e (I%) 247 (2) 153 (1) 138 (3) 136 (6) 135 (65) 134 (1) 133 (1)
128 (1) 127 (26) 126 (100) 125 (3) 124 (2) 112 (1) 110 (1)
105 (1) 97 (1) 96 (3) 92 (4) 86 (1) 85 (4) 83 (2) 82 (3)
79 (2) 78 (1) 77 (10) 71 (1) 70 (4) 69 (1) 68 (3) 67 (1)
65 (1) 64 (2) 58 (6) 56 (3) 55 (6) 53 (2) 51 (2) 46 (3)
45 (3) 44 (7) 43 (2) 42 (6) 41 (5) 39 (2) 38 (10) 36 (29)
35 (3) 32 (4) 31 (4) 28 (22).

m* 77, 56.5, 52.

1-(4-Chlorobenzamidomethyl)-cyclohexyldimethylamine (60)

m/e (I%) 141 (3) 139 (9) 127 (10) 126 (100) 113 (1) 111 (5) 84 (3)
77 (2) 75 (2) 55 (3) 44 (3) 42 (3) 41 (3) 37 (8) 36 (21)
32 (14).

1-(4-Methoxybenzamidomethyl)-cyclohexyldimethylamine (61)

m/e (I%) 245 (2) 147 (7) 136 (1) 135 (13) 127 (11) 126 (100) 125 (1)
124 (1) 108 (1) 96 (2) 92 (3) 84 (2) 82 (1) 81 (1) 79 (1)
78 (1) 77 (5) 70 (1) 68 (1) 64 (1) 58 (2) 56 (1) 55 (3)
44 (3) 42 (2) 41 (3) 39 (2) 38 (3) 36 (10) 35 (2) 32 (2)
28 (12).

m* 85.

1-(2-Naphthamidomethyl)-cyclohexyldimethylamine (62)

m/e (I%) 155 (3) 128 (1) 127 (10) 126 (85) 96 (1) 84 (8) 82 (1)
81 (2) 79 (2) 77 (2) 74 (3) 71 (2) 70 (3) 68 (2) 59 (2)
58 (6) 56 (3) 55 (6) 53 (2) 52 (2) 50 (7) 46 (3) 45 (4)
44 (10) 43 (2) 42 (7) 41 (6) 39 (2) 38 (32) 37 (5) 36 (100)
35 (15) 32 (2) 31 (3) 30 (2) 29 (4) 28 (10).

m* 52.

1-(4-Dimethylaminobenzamidomethyl)-cyclohexyldimethylamine (120)

m/e (I%) 258 (1) 193 (1) 165 (1) 164 (2) 148 (16) 127 (14) 126 (100)
125 (2) 124 (1) 120 (1) 119 (2) 105 (2) 104 (2) 96 (2)
91 (1) 84 (5) 82 (1) 81 (2) 79 (2) 78 (1) 77 (4) 71 (1)
70 (3) 68 (2) 58 (6) 55 (4) 53 (1) 46 (2) 45 (1) 44 (6)
43 (1) 42 (9) 41 (4) 39 (2) 38 (4) 36 (12) 35 (2) 31 (2)
30 (2) 29 (2) 28 (3).

1-(4-Bromobenzamidomethyl)-cyclohexyldimethylamine (63)

m/e (I%) 338 (1) 336 (1) 297 (1) 296 (4) 295 (1) 294 (4) 280 (1)
198 (2) 197 (15) 195 (15) 185 (5) 183 (5) 157 (3) 155 (3)
127 (10) 126 (100) 124 (1) 116 (1) 112 (1) 110 (2) 105 (2)
96 (2) 84 (2) 81 (2) 79 (2) 77 (3) 76 (4) 75 (3) 70 (2)
69 (2) 58 (2) 55 (4) 50 (2) 44 (3) 41 (5) 38 (8) 36 (21)
32 (6) 28 (30).

1-(3-Bromobenzamidomethyl)-cyclohexyldimethylamine (64)

m/e (I%) 185 (5) 183 (5) 157 (4) 155 (4) 127 (9) 126 (100) 96 (1)
84 (2) 81 (1) 76 (2) 75 (1) 70 (2) 68 (1) 58 (2) 56 (1)
55 (2) 46 (1) 44 (3) 42 (2) 41 (2) 38 (2) 36 (7) 35 (1)
31 (3) 30 (6) 29 (6) 28 (5).

1-(4-Hydroxybenzamidomethyl)-cyclohexyldimethylamine ethoxyformic ester (65)

m/e (I%) 127 (8) 126 (100) 121 (2) 96 (1) 84 (7) 81 (1) 80 (2)
79 (25) 78 (3) 71 (2) 70 (2) 68 (1) 66 (1) 65 (1) 64 (4)
58 (4) 56 (2) 55 (4) 53 (2) 52 (15) 51 (8) 50 (5) 49 (2)
46 (4) 45 (10) 44 (69) 43 (7) 42 (4) 41 (4) 39 (4) 38 (13)
37 (1) 36 (20) 35 (4) 32 (2) 31 (18) 30 (2) 29 (47) 28 (18).

m* 62, 34.3.

1-(4-Toluamidomethyl)-cyclohexyldimethylamine (122)

m/e (I%) 127 (8) 126 (100) 119 (4) 91 (4) 84 (1) 65 (1) 58 (1) 55 (1) 44 (1) 41 (1) 38 (1) 36 (3).

m* 77, 69.5, 52, 46.5.

1-(4-Ethoxybenzamidomethyl)-cyclohexyldimethylamine (121)

m/e (I%) 149 (3) 127 (1) 126 (100) 121 (4) 96 (1) 93 (2) 84 (2) 70 (2) 68 (1) 65 (3) 58 (3) 56 (1) 55 (3) 46 (1) 44 (4) 42 (2) 41 (2) 39 (2) 38 (3) 36 (9) 35 (1) 29 (2) 28 (2) 27 (1).

1-(3,4-Dichlorocinnamamidomethyl)-cyclohexyldimethylamine (66)

m/e (I%) 127 (13) 126 (100) 98 (4) 85 (8) 84 (100) 71 (32) 70 (6) 68 (3) 58 (9) 56 (11) 55 (7) 53 (3) 44 (10) 43 (4) 42 (19) 41 (11) 39 (8) 38 (6) 36 (17) 35 (4) 29 (5) 28 (7).

2-Ethylamino-2-methyl-3-phenylpropanonitrile (84a)

m/e (I%) 161 (3) 160 (1) 146 (1) 130 (1) 118 (1) 117 (3) 116 (1) 115 (3) 105 (3) 104 (1) 103 (1) 97 (2) 92 (3) 91 (16) 90 (2) 89 (2) 78 (1) 77 (3) 71 (5) 70 (93) 69 (1) 68 (1) 65 (6) 63 (3) 52 (1) 51 (4) 50 (1) 43 (3) 42 (100) 41 (4) 40 (1) 39 (5) 38 (3) 36 (8) 35 (1) 32 (2) 29 (7) 28 (8) 27 (23) 26 (3).

m* 113, 49.1(97→69), 46.5, 25.

3-(4-Chlorophenyl)-2-ethylamino-2-methylpropanonitrile (84b)

m/e (I%) 197 (1) 195 (4) 194 (1) 180 (1) 144 (2) 139 (3) 127 (4) 126 (1) 125 (10) 117 (1) 116 (2) 115 (3) 103 (1) 99 (2) 97 (3) 91 (2) 90 (2) 89 (5) 82 (2) 77 (1) 75 (2) 73 (1)

71 (6) 70 (96) 69 (2) 68 (2) 65 (1) 63 (4) 62 (1) 55 (1)
54 (2) 51 (2) 50 (1) 44 (1) 43 (4) 42 (100) 41 (4) 39 (4)
38 (4) 37 (11) 36 (1) 30 (1) 29 (8) 28 (4) 27 (21) 26 (3).

m* 89, 25.

2-Amino-2-methyl-3-phenylpropanonitrile (87a)

m/e (I%) 135 (2) 134 (22) 133 (5) 132 (2) 117 (1) 115 (1) 111 (1)
106 (1) 105 (2) 93 (2) 92 (33) 91 (70) 90 (3) 89 (5) 79 (1)
78 (10) 77 (7) 76 (1) 75 (1) 74 (8) 66 (1) 65 (17) 64 (2)
63 (7) 62 (2) 59 (14) 52 (3) 51 (9) 50 (5) 45 (10) 44 (21)
43 (100) 42 (17) 41 (10) 40 (5) 39 (14) 38 (3) 36 (2)
32 (9) 31 (42) 30 (1) 29 (10) 28 (27) 27 (13) 26 (3).

m* 90.3, 63.2, 46.5, 28.5.

2-(N-Carboethoxyamino)-2-methyl-3-phenylpropanonitrile (88)

m/e (I%) 233 (2) 232 (12) 187 (2) 186 (1) 185 (5) 160 (3) 158 (2)
157 (2) 145 (2) 144 (12) 143 (2) 142 (17) 118 (2) 117 (7)
116 (6) 115 (6) 105 (2) 104 (1) 103 (1) 93 (2) 92 (20)
91 (100) 90 (10) 89 (4) 78 (2) 77 (4) 69 (53) 65 (15)
64 (1) 62 (4) 61 (2) 56 (15) 53 (1) 52 (2) 51 (6) 50 (2)
45 (2) 44 (1) 43 (3) 42 (44) 41 (4) 40 (1) 39 (8) 31 (2)
29 (35) 28 (11) 27 (9) 26 (2).

m* 113, 90.3, 88.1(232→143), 49, 46.5, 35, 33.5(142→69),
25.5(69→42).

2-Amino-3-(3,4-dimethoxyphenyl)-2-methylpropanoic acid ethyl ester (89b)

m/e (I%) 267 (1) 195 (2) 194 (22) 178 (2) 153 (3) 152 (38) 151 (31)
138 (1) 137 (3) 126 (5) 121 (1) 118 (1) 117 (5) 116 (100)

108 (1) 107 (3) 106 (2) 105 (1) 97 (4) 91 (1) 90 (1) 89 (2)
88 (19) 79 (1) 78 (2) 77 (2) 70 (1) 65 (3) 57 (1) 56 (2)
51 (2) 47 (1) 43 (2) 42 (31) 41 (1) 39 (2) 29 (2) 28 (1)
27 (15).

m* 123.5, 86.5, 66.8, 55.5.

2-Amino-3-(4-chlorophenyl)-2-methylpropanonitrile (87b)

m/e (I%) 183 (3) 170 (3) 169 (3) 168 (8) 167 (8) 139 (2) 131 (1)
130 (1) 128 (4) 127 (10) 126 (14) 125 (25) 117 (2) 116 (3)
115 (3) 103 (2) 101 (1) 99 (4) 92 (2) 91 (16) 90 (5)
89 (23) 77 (2) 75 (3) 74 (8) 73 (3) 65 (3) 64 (2) 63 (10)
62 (3) 61 (1) 59 (11) 51 (5) 50 (4) 45 (10) 44 (4) 43 (100)
42 (39) 41 (11) 40 (6) 39 (9) 38 (3) 32 (48) 31 (92)
30 (6) 29 (36) 28 (15) 27 (15) 26 (3).

2-Amino-2-methyl-3-phenylpropanoic acid ethyl ester (89a)

m/e (I%) 135 (3) 134 (46) 119 (1) 118 (2) 117 (9) 116 (100) 115 (2)
106 (1) 105 (1) 92 (3) 91 (14) 89 (1) 88 (18) 79 (4)
78 (73) 77 (12) 76 (2) 75 (1) 74 (2) 70 (1) 67 (4) 65 (4)
63 (2) 57 (1) 56 (2) 52 (11) 51 (11) 50 (7) 47 (2) 45 (1)
44 (11) 43 (4) 42 (38) 41 (6) 40 (3) 39 (8) 38 (2) 37 (1)
32 (3) 31 (2) 29 (5) 28 (20) 27 (4) 26 (2).

m* 115, 113, 102, 76, 66.8(116→88), 55.8, 33.5.

2-Carboethoxyamino-2-methyl-3-phenylpropanoic acid ethyl ester (90a)

m/e (I%) 232 (2) 206 (6) 205 (40) 191 (8) 190 (25) 189 (11) 188 (100)
177 (1) 163 (1) 162 (9) 161 (2) 160 (5) 145 (3) 144 (3)
143 (3) 142 (27) 135 (4) 134 (19) 133 (3) 132 (3) 130 (1)
124 (2) 119 (3) 118 (4) 117 (14) 116 (57) 115 (8) 114 (6)

107 (2) 105 (2) 104 (1) 103 (1) 93 (2) 92 (13) 91 (65)
90 (3) 89 (4) 88 (26) 79 (2) 78 (2) 77 (4) 76 (15) 65 (12)
63 (3) 62 (1) 56 (3) 52 (1) 51 (4) 50 (1) 48 (3) 45 (3)
44 (5) 43 (6) 42 (80) 41 (6) 40 (2) 39 (6) 31 (4) 30 (2)
29 (62) 28 (5) 27 (14) 26 (4).

m* 107.3(188→142), 71.6(188→116), 28.8.

2-Carboethoxyamino-3-(3,4-dimethoxyphenyl)-2-methylpropanoic acid ethyl ester (90b)

m/e (I%) 339 (4) 294 (2) 265 (3) 249 (4) 224 (3) 220 (1) 194 (2)
189 (1) 188 (11) 153 (2) 152 (17) 151 (100) 142 (8) 138 (1)
137 (5) 135 (2) 121 (2) 117 (1) 116 (13) 114 (1) 108 (2)
107 (5) 106 (4) 105 (2) 91 (3) 90 (3) 89 (2) 88 (9) 79 (2)
78 (4) 77 (3) 70 (6) 65 (4) 51 (3) 45 (2) 44 (2) 43 (2)
42 (33) 41 (2) 39 (3) 31 (3) 29 (34) 28 (11) 27 (7).

m* 184.4(339→250), 107.3(188→142), 71.6(188→116).

2-Piperidinomethyl-1-indanone (106c)

m/e (I%) 230 (8) 229 (44) 228 (4) 145 (3) 144 (25) 132 (3) 117 (2)
116 (10) 115 (18) 104 (2) 99 (3) 98 (46) 97 (7) 96 (2)
89 (2) 86 (3) 85 (54) 84 (100) 83 (1) 82 (2) 77 (1) 76 (1)
70 (9) 69 (1) 68 (1) 67 (1) 65 (1) 63 (3) 58 (3) 57 (27)
56 (27) 55 (12) 54 (3) 53 (2) 52 (1) 51 (3) 50 (2) 45 (2)
44 (32) 43 (23) 42 (29) 41 (18) 40 (2) 39 (33) 38 (25)
37 (2) 36 (22) 35 (6) 32 (3) 30 (32) 29 (29) 28 (30) 27 (16)
26 (3).

m* 114(116→115), 93.4(144→116), 55,37.

2-Dimethylaminomethyl-1-indanone (106a)

m/e (I%) 145 (2) 144 (8) 117 (1) 116 (5) 115 (10) 98 (1) 91 (1)
89 (2) 77 (1) 63 (2) 59 (2) 58 (92) 57 (3) 51 (1) 50 (1)
45 (29) 44 (100) 43 (7) 42 (11) 41 (2) 40 (2) 39 (2) 38 (15)
37 (1) 36 (89) 35 (5) 32 (2) 30 (4) 28 (15) 27 (2).

m* 114(116→115), 93.4(144→116).

2-Morpholinomethyl-1-indanone (106d)

m/e (I%) 200 (4) 146 (2) 145 (5) 144 (17) 132 (2) 131 (2) 130 (1)
117 (3) 116 (10) 115 (22) 103 (1) 102 (1) 101 (6) 100 (100)
99 (6) 98 (3) 97 (3) 90 (1) 89 (3) 87 (5) 86 (8) 77 (2)
76 (1) 75 (1) 73 (2) 72 (2) 71 (2) 70 (1) 65 (2) 63 (3)
62 (1) 59 (2) 58 (25) 57 (8) 56 (9) 55 (1) 51 (2) 50 (2)
46 (7) 45 (22) 44 (6) 43 (6) 42 (9) 41 (3) 39 (2) 38 (7)
36 (25) 35 (2) 32 (3) 31 (44) 30 (13) 29 (7) 28 (17)
27 (12) 26 (3).

m* 114(116→115), 113, 93.4(144→116).

2-Diethylaminomethyl-1-indanone (106b)

m/e (I%) 144(4) 116 (2) 115 (6) 86 (2) 73 (18) 72 (11) 59 (2)
58 (100) 57 (2) 56 (3) 44 (23) 43 (1) 42 (4) 41 (2) 38 (2)
37 (1) 36 (45) 35 (2) 30 (68) 29 (7) 28 (5) 27 (4).

m* 114(116→115), 93.4(144→116), 46.3.

2-N^4-Methylpiperazinomethyl-1-indanone (106e)

m/e (I%) 243 (6) 225 (1) 145 (2) 144 (8) 128 (8) 127 (5) 116 (6)
115 (10) 114 (3) 113 (21) 112 (2) 111 (2) 101 (1) 100 (21)
99 (3) 98 (3) 89 (2) 83 (1) 82 (3) 80 (4) 71 (3) 70 (15)

63 (2) 59 (3) 58 (77) 57 (9) 56 (14) 55 (4) 54 (3) 51 (2)
50 (2) 45 (2) 44 (12) 43 (36) 42 (34) 41 (6) 40 (1) 39 (3)
38 (32) 37 (3) 36 (100) 35 (12) 32 (10) 30 (7) 29 (7)
28 (68) 27 (11) 26 (3).

m* 114(116→115).

2-Methyl-2-N^4-methylpiperazinomethyl-1-indanone (107e)

m/e (I%) 171 (1) 170 (16) 147 (3) 146 (41) 145 (13) 144 (3) 132 (3)
131 (33) 129 (2) 128 (2) 127 (8) 118 (4) 117 (6) 116 (5)
115 (10) 114 (13) 113 (71) 112 (4) 111 (5) 105 (14) 103 (6)
100 (34) 99 (5) 98 (5) 97 (2) 91 (3) 89 (2) 85 (3) 84 (3)
77 (8) 76 (2) 72 (2) 71 (10) 70 (40) 63 (2) 59 (2) 58 (57)
57 (11) 56 (27) 55 (7) 54 (2) 51 (4) 50 (2) 44 (13) 43 (49)
42 (28) 41 (7) 39 (4) 38 (26) 37 (3) 36 (100) 35 (8)
32 (3) 30 (5) 29 (5) 28 (17) 27 (7).

m* 114(116→115), 43.5.

2-Methyl-2-morpholinomethyl-1-indanone (107d)

m/e (I%) 245 (2) 159 (1) 158 (2) 146 (3) 145 (3) 144 (4) 143 (1)
132 (1) 131 (7) 130 (2) 129 (4) 128 (4) 127 (2) 119 (1)
118 (2) 117 (6) 116 (13) 105 (9) 103 (2) 102 (3) 101 (41)
100 (100) 99 (7) 98 (10) 91 (10) 90 (2) 89 (3) 87 (5)
86 (3) 78 (2) 77 (10) 76 (1) 72 (2) 71 (3) 70 (7) 69 (1)
68 (1) 65 (3) 64 (1) 63 (3) 58 (1) 57 (9) 56 (44) 55 (4)
54 (2) 53 (2) 51 (5) 50 (2) 45 (2) 44 (2) 43 (8) 42 (26)
41 (8) 40 (1) 39 (5) 38 (12) 37 (1) 36 (44) 35 (3) 32 (5)
30 (6) 29 (9) 28 (30) 27 (6).

m* 114(116→115), 49.5, 48.5, 31.4.

2-Methyl-2-piperidinomethyl-1-indanone (107c)

m/e (I%) 243 (1) 159 (1) 158 (2) 147 (2) 146 (16) 145 (5) 144 (7)
143 (1) 132 (2) 131 (19) 130 (2) 129 (4) 128 (4) 127 (2)
118 (2) 117 (5) 116 (7) 115 (20) 110 (2) 106 (1) 105 (8)
104 (1) 103 (4) 102 (1) 100 (2) 99 (33) 98 (100) 97 (7)
96 (7) 91 (12) 90 (2) 89 (3) 87 (3) 86 (52) 85 (3) 84 (7)
83 (1) 82 (1) 78 (2) 77 (7) 76 (2) 75 (1) 72 (1) 70 (3)
69 (5) 68 (2) 65 (3) 64 (1) 63 (3) 58 (7) 57 (3) 56 (5)
55 (17) 54 (2) 53 (2) 51 (4) 50 (2) 44 (8) 43 (5) 42 (18)
41 (19) 40 (1) 39 (6) 38 (8) 37 (1) 36 (39) 35 (3) 30 (10)
29 (6) 28 (9) 27 (5) 26 (2).

m* 114(116→115), 94, 50.

2-Diethylaminomethyl-2-methyl-1-indanone (107b)

m/e (I%) 146 (1) 144 (1) 131 (2) 116 (1) 115 (2) 105 (1) 91 (2)
87 (5) 86 (100) 77 (1) 71 (2) 58 (2) 56 (2) 44 (1) 42 (2)
38 (2) 36 (4) 30 (100) 29 (3) 28 (2) 27 (1).

m* 114(116→115), 94, 39.2.

2-Dimethylaminomethyl-2-methyl-1-indanone (107a)

m/e (I%) 203 (3) 176 (4) 161 (3) 160 (1) 159 (7) 158 (4) 154 (1)
147 (3) 146 (13) 145 (6) 144 (5) 143 (2) 134 (1) 132 (2)
131 (10) 130 (3) 129 (6) 128 (5) 127 (2) 122 (1) 118 (3)
117 (5) 116 (8) 115 (20) 114 (1) 106 (2) 105 (26) 103 (2)
102 (2) 92 (1) 91 (9) 90 (2) 89 (4) 84 (1) 78 (3) 77 (14)
76 (2) 75 (1) 74 (1) 71 (1) 70 (1) 65 (4) 64 (2) 63 (4)
62 (1) 59 (26) 58 (100) 57 (10) 56 (2) 53 (2) 50 (3)
49 (1) 46 (5) 45 (100) 44 (100) 43 (50) 42 (100) 41 (23)
40 (11) 39 (28) 38 (65) 37 (7) 36 (100) 35 (18) 32 (3)

30 (40) 29 (100) 28 (40) 27 (16).

m* 128, 114(116→115), 88.

3-Methyl-1-oxo-3-piperidinomethyl-1,2,3,4-tetrahydroisoquinoline (109c)

m/e (I%) 162 (2) 161 (2) 160 (2) 157 (2) 146 (6) 145 (2) 144 (1) 133 (1) 132 (1) 131 (6) 130 (1) 129 (1) 121 (4) 118 (3) 117 (2) 116 (2) 115 (4) 105 (9) 103 (2) 99 (7) 98 (100) 97 (2) 96 (3) 93 (2) 91 (4) 90 (2) 89 (1) 88 (2) 85 (2) 84 (7) 83 (1) 78 (2) 77 (7) 76 (1) 73 (2) 70 (3) 69 (3) 65 (1) 64 (7) 63 (2) 61 (2) 60 (1) 59 (2) 58 (2) 57 (3) 56 (4) 55 (6) 51 (4) 50 (2) 48 (2) 45 (13) 44 (7) 43 (22) 42 (5) 41 (7) 39 (4) 38 (1) 36 (4) 32 (6) 31 (2) 30 (3) 29 (4) 28 (38) 27 (5).

3-Methyl-3-morpholinomethyl-1-oxo-1,2,3,4-tetrahydroisoquinoline (109d)

m/e (I%) 161 (1) 160 (11) 159 (3) 142 (1) 127 (1) 101 (12) 100 (100) 77 (1) 56 (5) 42 (3) 28 (2).

m* 126(160→142), 93.1(142→115), 49.5, 48.5, 31.4.

3-Dimethylaminomethyl-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline (109a)

m/e (I%) 161 (1) 160 (11) 159 (4) 142 (2) 115 (1) 91 (1) 90 (1) 89 (1) 59 (10) 58 (100) 42 (4) 30 (1) 28 (1).

m* 160, 138, 126(160→142), 113, 93.1(142→115), 89, 66.8(118→90), 68.9(115→89).

3-Diethylaminomethyl-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline (109b)

m/e (I%) 247 (6) 246 (3) 234 (2) 233 (6) 232 (3) 229 (3) 228 (2)
213 (7) 174 (5) 173 (3) 162 (5) 161 (4) 160 (21) 159 (11)
158 (6) 157 (13) 148 (2) 147 (4) 146 (6) 145 (3) 144 (2)
143 (5) 133 (5) 132 (3) 131 (10) 130 (7) 129 (6) 128 (5)
127 (3) 119 (2) 118 (9) 117 (6) 116 (7) 115 (11) 113 (6)
112 (2) 106 (2) 105 (23) 104 (3) 103 (5) 102 (2) 100 (8)
98 (4) 91 (15) 90 (14) 89 (11) 88 (3) 87 (91) 86 (100)
85 (6) 84 (7) 79 (2) 78 (4) 77 (27) 76 (3) 75 (2) 73 (2)
72 (22) 71 (4) 70 (6) 65 (5) 64 (3) 63 (7) 59 (2) 58 (80)
57 (11) 56 (23) 55 (4) 54 (3) 53 (2) 52 (2) 51 (11) 50 (4)
44 (8) 43 (13) 42 (34) 41 (11) 40 (3) 39 (10) 32 (9)
30 (100) 29 (34) 28 (57) 27 (15) 26 (4).

m* 126(160→142), 93.1(142→115), 39.3.

3-Methyl-3-N^4-methylpiperazinomethyl-1-oxo-1,2,3,4-tetrahydroisoquinoline (109e)

m/e (I%) 273 (5) 255 (4) 212 (1) 211 (2) 203 (2) 197 (2) 185 (1)
184 (2) 183 (1) 161 (2) 160 (4) 159 (1) 158 (2) 157 (4)
156 (3) 150 (2) 146 (4) 145 (2) 144 (2) 143 (2) 142 (2)
139 (1) 137 (1) 133 (3) 132 (2) 131 (4) 130 (3) 129 (2)
128 (2) 125 (2) 123 (2) 119 (1) 118 (6) 117 (4) 116 (6)
115 (4) 114 (12) 113 (100) 112 (2) 111 (5) 110 (2) 109 (3)
105 (4) 104 (2) 103 (2) 100 (2) 99 (8) 98 (8) 97 (6) 96 (3)
95 (5) 93 (3) 91 (4) 90 (4) 89 (3) 85 (3) 84 (2) 83 (5)
82 (3) 81 (4) 80 (1) 79 (1) 78 (1) 77 (5) 76 (1) 72 (1)
70 (44) 69 (6) 68 (1) 67 (3) 65 (2) 63 (2) 59 (1) 58 (10)
57 (8) 56 (10) 55 (8) 54 (2) 53 (1) 51 (3) 50 (2) 44 (1)

43 (18) 42 (19) 41 (7) 39 (4).

m* 126(160→142), 93.1(142→115), 43.4.

3-Dimethylaminomethyl-1-oxo-1,2,3,4-tetrahydroisoquinoline (108a)

m/e (I%) 59 (4) 58 (100) 42 (2) 30 (1).

m* 145.5, 128, 112.2(146→128), 95.4(145→118), 88.5, 68.8(118→90), 56.5, 46.5, 32.

3-N^4-Methylpiperazinomethyl-1-oxo-1,2,3,4-tetrahydroisoquinoline (108e)

m/e (I%) 146 (1) 128 (2) 114 (7) 113 (100) 111 (1) 98 (3) 91 (2) 90 (1) 89 (1) 71 (3) 70 (40) 58 (3) 57 (1) 56 (3) 44 (2) 43 (6) 42 (11) 41 (1) 28 (2) 27 (1).

m* 112.2(146→128), 43.4.

3-Morpholinomethyl-1-oxo-1,2,3,4-tetrahydroisoquinoline (108d)

m/e (I%) 146 (1) 128 (2) 101 (6) 100 (100) 91 (2) 89 (1) 70 (1) 56 (10) 43 (2) 42 (5) 41 (2) 39 (1) 30 (2) 29 (2) 28 (5) 27 (1).

m* 112.2(146→128), 88.5, 59.5, 58.5, 31.4.

3-Diethylaminomethyl-1-oxo-1,2,3,4-tetrahydroisoquinoline (108b)

m/e (I%) 128 (1) 91 (1) 87 (5) 86 (100) 58 (3) 38 (1) 36 (4) 32 (2) 30 (2) 28 (10).

m* 112.2(146→128), 39.2.

1-Oxo-3-piperidinomethyl-1,2,3,4-tetrahydroisoquinoline (108c)

m/e (I%) 146 (1) 145 (3) 144 (13) 118 (2) 117 (2) 116 (11) 115 (20)
113 (6) 112 (2) 105 (2) 104 (2) 99 (5) 98 (67) 97 (4)
96 (4) 91 (4) 90 (2) 89 (4) 85 (33) 84 (65) 83 (3) 82 (3)
78 (2) 77 (3) 76 (2) 75 (2) 74 (1) 70 (9) 69 (3) 68 (3)
67 (2) 65 (2) 63 (5) 62 (2) 58 (2) 57 (31) 56 (33) 55 (14)
54 (4) 53 (3) 52 (2) 51 (5) 50 (4) 44 (22) 43 (16) 42 (25)
41 (17) 40 (2) 39 (14) 38 (2) 32 (18) 30 (19) 29 (18)
28 (100) 27 (14) 26 (3).

m* 112.2(146→128), 83, 55.1.

SECTION IV

PHARMACOLOGICAL RESULTS

In the following reports standard notation is used to indicate activity levels.

++ = marked activity

\+ = moderate activity

$\overset{+}{-}$ = negligible activity

\- = inactive

TABLE 14

1-(SUBSTITUTED-BENZAMIDOMETHYL)-CYCLOHEXYLDIMETHYLAMINES

ROUTE	TEST AND DOSE	COMPOUNDS (53)	(54)	(55)
ORAL	1. Effects on behaviour in mouse 100 mg/Kg	+	±	±
ORAL	2. LD_{50} mg/Kg $>$ 100			
ORAL	3. Effects on body temperature 100 mg/Kg	±	-	+
ORAL	4. Antimaximal electroshock 100 mg/Kg	-	-	-
ORAL	5. Antagonism of leptazol induced convulsions 100 mg/Kg	-	-	-
S.C.	6. Hot-plate a) Direct effect	++	++	++
	100 mg/Kg b) Interact.morphine	-	-	-
ORAL	7. Effects on phenylquinone induced writhing 100 mg/Kg	+	++	++
ORAL	8. Effects on central cholinergic mechanism a) Tremor	-	+/++	-
	50 mg/Kg b) Hypothermia	-	-	-

Remarks:- a) Compound (53) produced Straub tail, fast gait and raised posture in test 1. Compound (55) produces unsteady gait, reduced reactivity and reduced response to pain in test 1.

b) Compounds (53) and (55) induced hyperthermia of 6.5° and 2° respectively in test 3.

c) Compound (53) completely abolished the reflex response of a mouse placed on a hot-plate in test 6a and compounds (54) and (55) also produced 100% inhibition and the animals were incapacitated.

d) Compound (53) inhibited writhes in test 7 and was further investigated. Compound (54) $\gg$ aspirin in test 7 and was investigated further. Compound (55) has activity

TABLE 14 (cont.)

≫aspirin in test 7 and was investigated further.

TABLE 15

1-(SUBSTITUTED-BENZAMIDOMETHYL)-CYCLOHEXYLDIMETHYLAMINES

ROUTE	TEST AND DOSE	COMPOUNDS (57)	(58)	(59)
ORAL	1. Effects on behaviour in mouse 100 mg/Kg	-	±	-
ORAL	2. LD_{50} mg/Kg $>$ 100			
ORAL	3. Effects on body temperature 100 mg/Kg	±	-	-
ORAL	4. Antimaximal electroshock 50 mg/Kg	-	-	-
ORAL	5. Antagonism of leptazol induced convulsions 50 mg/Kg	-	±	±
S.C.	6. Hot-plate a) Direct effect	++	±	++
ORAL	50 mg/Kg b) Interact. morphine	-	-	-
ORAL	7. Effects on phenylquinone induced writhing 50 mg/Kg	++	-	-

Remarks:- a) Compound (58) produced high posture in test 1.

b) Compound (57) induced hyperthermia of 0.7^{o} in test 3.

c) Compounds (57) and (59) produced 100% inhibition in test 6a.

d) Compound (57) was $\simeq$ codeine in test 7 and was investigated further.

TABLE 16

1-(SUBSTITUTED-BENZAMIDOMETHYL)-CYCLOHEXYLDIMETHYLAMINES

ROUTE	TEST AND DOSE	COMPOUNDS (61)	(62)	(63)
ORAL	1. Effects on behaviour in mouse 100 mg/Kg	±	±	+
ORAL	2. LD_{50} mg/Kg $>$ 100			
ORAL	3. Effects on body temperature 100 mg/Kg	±	±	±
ORAL	4. Effects on pupil diameter 100 mg/Kg	-	-	++
ORAL	5. Antimaximal electroshock 50 mg/Kg	-	-	-
S.C.	6. Antagonism of leptazol induced convulsions 50 mg/Kg	-	-	-
S.C.	7. Hot-plate a) Direct effect	++	++	++
S.C.	50 mg/Kg b) Interact. morphine	-	-	-
ORAL	8. Effects on phenylquinone induced writhing 50 mg/Kg	-	-	++

Remarks:- a) Compound (61) produced low posture in test 1. Compound (62) produced limb splay and Straub tail in test 1. Compound (63) produced Straub tail, raised posture and marked inhibition of pain response in test 1.

b) Compounds (62) and (63) induced hyperthermia of 0.8° in test 3. Compound (61) induced hypothermia of 0.5° in test 3.

c) Compound (63) produced marked mydriasis in test 3.

d) Compounds (61), (62) and (63) produced 100% inhibition in test 7a.

e) Compound (63) was $>$ codeine and completely abolished writhing in test 8. Compound (63) was investigated further.

TABLE 17

1-(SUBSTITUTED-BENZAMIDOMETHYL)-CYCLOHEXYLDIMETHYLAMINES

ROUTE	TEST AND DOSE	COMPOUNDS (64)	(65)	(66)
ORAL	1. Effects on behaviour in mouse 100 mg/Kg	±	±	±
ORAL	2. LD_{50} mg/Kg $>$ 100			
ORAL	3. Effects on body temperature 100 mg/Kg	-	-	±
ORAL	4. Effects on pupil diameter 100 mg/Kg	±/+	-	-
ORAL	5. Antimaximal electroshock 50 mg/Kg	-	-	-
S.C.	6. Antagonism of leptazol induced convulsions 50 mg/Kg	-	-	-
S.C.	7. Hot-plate a) Direct effect	++	+	++
S.C.	50 mg/Kg b) Interact. morphine	-	-	-
ORAL	8. Effects on phenylquinone induced writhing 50 mg/Kg	++	-	-

Remarks:- a) Compound (64) produced Straub tail, compound (65) Straub tail and raised posture and compound (66) limb splay in test 1.

b) Compound (66) induced hyperthermia of 0.5^{o} in test 3.

c) Compound (64) produced moderate mydriasis in test 4.

d) Compounds (64) and (66) produced 100% inhibition in test 7a.

e) Compound (64) was $>$ codeine and writhing was almost abolished in test 8. Compound (64) was investigated further.

SECONDARY INVESTIGATION OF THE ANALGETIC ACTIVITY OF 1 - (SUBSTITUTED-BENZAMIDOMETHYL)-CYCLOHEXYLDIMETHYLAMINES.

Compound (53)

a) Hot-plate test:-

Subcutaneous ED_{50} value = 15.5(5.36 - 42.0)mg/Kg

Subcutaneous morphine ED_{50} values = 2.2(1.23 - 5.95)mg/Kg

b) Phenylquinone test:-

Oral ED_{50} value = 15.3mg/Kg

Aspirin oral ED_{50} values = 33.9(14.0 - 70.0)mg/Kg

Compound (54)

a) Hot-plate test:-

Subcutaneous ED_{50} value = 9.7mg/Kg

b) Phenylquinone test:-

Oral ED_{50} value = 5 - 200mg/Kg

Compound (55)

a) Hot-plate test:-

Subcutaneous ED_{50} value = 2.5mg/Kg

b) Phenylquinone test:-

Oral ED_{50} value = 0.85mg/Kg

Compound (57)

a) Hot-plate test:-

Subcutaneous ED_{50} value = 21.0(14.0 - 31.5)mg/Kg

Oral ED_{50} value = 5.4(2.1 - 10.2)mg/Kg

b) Phenylquinone test:-

Oral ED_{50} value = 30.0(11.0 - 78.0)mg/Kg

Compound (63)

a) Hot-plate test:-

Subcutaneous ED_{50} value = 1.2(wide limits)mg/Kg

b) Phenylquinone test:-

Oral ED_{50} value = 7.0(3.4 - 16.1)mg/Kg

Compound (64)

a) Hot-plate test:-

Subcutaneous ED_{50} value = 7.2(3.2 - 15.8)mg/Kg

b) Phenylquinone test:-

Oral ED_{50} value = 10.0(4.2 - 24.0)mg/Kg

TABLE 18

2-DIETHYLAMINOMETHYL-2-METHYL-1-INDANONE (107b)

TEST	DOSE μM/Kg	EFFECTS						SUMMARY
		REACTION TIMES			BEHAVIOUR			
		TEST	SALINE	REFERENCE DRUG	DEP	NORM	STIM	
Hot-plate 55°C	200 S.C.	8,10,12 $\xi x = 30$	10,12,13 $\xi x = 35$	codeine 150μM/Kg		✓		-
				30,45, 60 $\xi x = 135$				
Hot-plate 59°C (interact. with morphine 50μM/Kg)	200 S.C.	all 3 >40 $\xi x = 120$	5,7,7 $\xi x = 19$	morphine 50μM/Kg		✓		-
				all 3>40 $\xi x = 120$				
				morphine pentaz. 150μM/Kg				
				12,14,21 $\xi x = 47$				
Phenyl-quinone (10μM/Kg I.P.)	400 S.C.	Total number of writhes				✓		±
		TEST	WATER	CODEINE 40μM/Kg				
		160 % inhib. = 30.7	231	128 % inhib. = 45.0				
Toxicity	200 S.C.	No. dead = 0 out of 3 S.C. LD_{50} > 200 M/Kg						

TABLE 19

2-METHYL-2-(N^4-METHYLPIPERAZINOMETHYL)-1-INDANONE (107e)

TEST	DOSE mg/Kg	EFFECTS						SUMMARY
		REACTION TIMES			BEHAVIOUR			
		TEST	SALINE	REFERENCE DRUG	DEP	NORM	STIM	
Hot-plate 55°C	50 S.C.	33,40,40 $\xi x = 113$	8,12,14 $\xi x = 34$	codeine 50mg/Kg		✓		++
				32,55,>60 $\xi x = 147$				
Hot-plate 59°C (interact. with morphine 15mg/Kg)	50 S.C.	all 3 >40 $\xi x = 120$	5,7,10 $\xi x = 22$	morphine 15mg/Kg		✓		-
				all 3>40 $\xi x = 120$				
				morphine + pentaz. 40mg/Kg				
				15,17,19 $\xi x = 51$				
Phenyl-quinone (2mg/Kg I.P.)	100 P.C.	Total number of writhes			✓			++
		TEST	WATER	CODEINE 10mg/Kg				
		4 % inhib. = 98.5	259	60 % inhib. = 76.8				
Toxicity	50 S.C.	No. dead = 0 out of 3 S.C. LD_{50} >50mg/Kg						

Remarks:- a) Compound (107e) caused convulsions in the hot-plate test when administered in a dose of 100mg/Kg S.C. but all the mice recovered. An ED_{50} value was obtained in the hot-plate test:-

= 27(18.8 - 52.6) mg/Kg

codeine = 14(7.3 - 26.6) mg/Kg.

b) Insufficient material was available for an ED_{50} evaluation in the phenylquinone test.

TABLE 19 (cont.)

c) Compound (107e) caused depressed behaviour in the phenylquinone test.

TABLE 20

2-PIPERIDINOMETHYL-1-INDANONE (106c)

TEST	DOSE μM/Kg	EFFECTS						SUMMARY
		REACTION TIMES			BEHAVIOUR			
		TEST	SALINE	REFERENCE DRUG	DEP	NORM	STIM	
Hot-plate 55°C	200 S.C.	Dead $\Sigma x = -$	10,12,13 $\Sigma x = 35$	codeine 150μM/Kg				Toxic
				30,45,>60 $\Sigma x = 135$				
Hot-plate 59°C (interact. with morphine 50μM/Kg)	200 S.C.	Dead $\Sigma x = -$	5,7,7 $\Sigma x = 19$	morphine 50μM/Kg				Toxic
				all 3>40 $\Sigma x = 120$				
				morphine + pentaz. 150μM/Kg				
				12,14,21 $\Sigma x = 47$				
Phenyl-quinone (10μM/Kg I.P.)	400 P.C.	Total number of writhes			✓			Toxic
		TEST	WATER	CODEINE 40μM/Kg				
		59 2/3 toxic	231	128 % inhib. = 45.0				
Toxicity	200 S.C.	No. dead = 3 out of 3			S.C. $LD_{50} < 200$μM/Kg			

Remarks:- a) Compound (106c) caused depressed behaviour in the phenylquinone test.

TABLE 21

3-DIMETHYLAMINOMETHYL-3-METHYL-1-OXO-1,2,3,4-TETRAHYDRO-ISOQUINOLINE (109a)

TEST	DOSE μM/Kg	EFFECTS						SUMMARY
		REACTION TIMES			BEHAVIOUR			
		TEST	SALINE	REFERENCE DRUG	DEP	NORM	STIM	
Hot-plate 55°C	200 S.C.	7,10,17 Ex = 34	13,15,16 Ex = 44	codeine 150μM/Kg		✓		-
				40,50,>60 Ex = 150				
Hot-plate 59°C (interact. with morphine 50μM/Kg)	200 S.C.	all 3 >40 Ex = 120	8,8,9 Ex = 25	morphine 50μM/Kg		✓		-
				all 3>40 Ex = 120				
				morphine + pentaz. 150μM/Kg				
				10,11,14 Ex = 35				
Phenyl-quinone (10μM/Kg I.P.)	400 P.C.	Total number of writhes				✓		±
		TEST	WATER	CODEINE 30μM/Kg				
		63 % inhib. = 37	100	46 % inhib. = 54				
Toxicity	200 S.C.	No. dead = 0 out of 3			S.C. LD_{50} >200μM/Kg			

TABLE 22

3-METHYL-3-PIPERIDINOMETHYL-1-OXO-1,2,3,4-TETRAHYDROISOQUINOLINE (109c)

TEST	DOSE mg/Kg	EFFECTS						SUMMARY
		REACTION TIMES			BEHAVIOUR			
		TEST	SALINE	REFERENCE DRUG	DEP	NORM	STIM	
Hot-plate 55°C	50 S.C.	11,17,17 $\Sigma x = 45$	9,13,15 $\Sigma x = 37$	codeine 50mg/Kg 30,>60,>60 $\Sigma x = 150$		✓		-
Hot-plate 59°C (interact. with morphine 15mg/Kg)	50 S.C.	25,>40, >40 $\Sigma x = 105$	8,10,11 $\Sigma x = 29$	morphine 15mg/Kg		✓		±
				all 3 >40 $\Sigma x = 120$				
				morphine + pentaz. 40mg/Kg				
				11,15,19 $\Sigma x = 45$				
Phenyl-quinone (2mg/Kg I.P.)	100 P.C.	Total number of writhes				✓		+
		TEST	WATER	CODEINE 10mg/Kg				
		136 % inhib. = 49.1	267	120 % inhib. = 55.1				
Toxicity	50 S.C.	No. dead = 0 out of 3			S.C. $LD_{50} > 50$mg/Kg			

Remarks:- a) Compound (109c) is being further investigated using the adjuvant arthritis test.

TABLE 23

3-METHYL-3-MORPHOLINOMETHYL-1-OXO-1,2,3,4-TETRAHYDROISOQUINOLINE (109d)

TEST	DOSE µM/Kg	EFFECTS						SUMMARY
		REACTION TIMES			BEHAVIOUR			
		TEST	SALINE	REFERENCE DRUG	DEP	NORM	STIM	
Hot-plate 55°C	200 S.C.	10,22,25 Ex = 57	10,12,13 Ex = 35	codeine 150µM/Kg		✓		+
				30,45, >60 Ex = 135				
Hot-plate 59°C (interact. with morphine 50µM/Kg)	200 S.C.	all 3 >40 Ex = 120	5,7,7 Ex = 19	morphine 50µM/Kg		✓		-
				all 3 >40 Ex = 120				
				morphine + pentaz. 150µM/Kg				
				12,14,21 Ex = 47				
Phenyl-quinone (10µM/Kg I.P.)	400 P.C.	Total number of writhes				✓		+
		TEST	WATER	CODEINE 40 M/Kg				
		99 % inhib. = 57.1	231	128 % inhib. = 45.0				
Toxicity	200 S.C.	No. dead = 0 out of 3			S.C. LD_{50} >200µM/Kg			

Remarks:- a) An ED_{50} evaluation was carried out on compound (109d) in the hot-plate test:

ED_{50} value = 419(220.4 - 796)µM/Kg

codeine ED_{50} value = 76.8(46 - 127)µM/Kg.

b) An ED_{50} evaluation was carried out on compound (109d) in the phenylquinone test:

ED_{50} value = 448(incalculable limits)µM/Kg

codeine ED_{50} value = 19(8.0 - 45.4)µM/Kg.

TABLE 24

1-OXO-3-PIPERIDINOMETHYL-1,2,3,4-TETRAHYDROISOQUINOLINE (108c)

TEST	DOSE μM/Kg	EFFECTS						SUMMARY
		REACTION TIMES			BEHAVIOUR			
		TEST	SALINE	REFERENCE DRUG	DEP	NORM	STIM	
Hot-plate 55°C	200 S.C.	6,8,10 Ex = 24	10,12,13 Ex = 35	codeine 150μM/Kg		✓		-
				30,45, >60 Ex = 135				
Hot-plate 59°C (interact. with morphine 50μM/Kg)	200 S.C.	22,>40, >40 Ex = 102	5,7,7 Ex = 19	morphine 50μM/Kg		✓		±
				all 3 >40 Ex = 120				
				morphine + pentaz. 150μM/Kg				
				12,14,21 Ex = 47				
Phenyl-quinone (10μM/Kg I.P.)	400 P.C.	Total number of writhes				✓		-
		TEST	WATER	CODEINE 40μM/Kg				
		227 % inhib. = 1.7	231	128 % inhib. = 45.0				
Toxicity	200 S.C.	No. dead = 0 out of 3			S.C. LD_{50} > 200μM/Kg			

TABLE 25

3-DIMETHYLAMINOMETHYL-1-OXO-1,2,3,4-TETRAHYDROISOQUINOLINE (108a)

TEST	DOSE mg/Kg	EFFECTS						SUMMARY
		REACTION TIMES			BEHAVIOUR			
		TEST	SALINE	REFERENCE DRUG	DEP	NORM	STIM	
Hot-plate 55°C	50 S.C.	9,11,13 Ex = 33	9,13,15 Ex = 37	codeine 50mg/Kg		✓		-
				30,>60,>60 Ex = 150				
Hot-plate 59°C (interact. with morphine 15mg/Kg)	50 S.C.	all 3 >40 Ex = 120	8,10,11 Ex = 29	morphine 15mg/Kg		✓		-
				all 3 >40 Ex = 120				
				morphine + pentaz. 40mg/Kg				
				11,15,19 Ex = 45				
Phenyl-quinone (2mg/Kg I.P.)	100 P.C.	Total number of writhes				✓		++
		TEST	WATER	CODEINE 10mg/Kg				
		79 % inhib. = 70.1	267	120 % inhib. = 55.1				
Toxicity	50 S.C.	No. dead = 0 out of 3		S.C. LD_{50} >50mg/Kg				

Remarks:- a) Compound (108a) is being further investigated using the adjuvant arthritis test.

TABLE 26

3-MORPHOLINOMETHYL-1-OXO-1,2,3,4-TETRAHYDROISOQUINOLINE (108d)

TEST	DOSE mg/Kg	EFFECTS						SUMMARY
		REACTION TIMES			BEHAVIOUR			
		TEST	SALINE	REFERENCE DRUG	DEP	NORM	STIM	
Hot-plate 55°C	50 S.C.	8,10,12 $\Sigma x = 30$	9,13,15 $\Sigma x = 37$	codeine 50mg/Kg		✓		-
				30,>60,>60 $\Sigma x = 150$				
Hot-plate 59°C (interact. with morphine 15mg/Kg)	50 S.C.	all 3 >40 $\Sigma x = 120$	8,10,11 $\Sigma x = 29$	morphine 15mg/Kg		✓		-
				all 3 >40 $\Sigma x = 120$				
				morphine + pentaz. 40mg/Kg				
				11,15,19 $\Sigma x = 45$				
Phenyl-quinone (2mg/Kg I.P.)	100 P.C.	Total number of writhes				✓		++
		TEST	WATER	CODEINE 10mg/Kg				
		51 % inhib. = 80.9	267	120 % inhib. = 55.1				
Toxicity	50 S.C.	No. dead = 0 out of 3 S.C. LD_{50} >50mg/Kg						

Remarks:- a) An ED_{50} evaluation was carried out on compound (108d) in the phenylquinone test:

ED_{50} value = 210(45.7 - 966)mg/Kg

codeine ED_{50} value = 5.7(2.4 - 13.6)mg/Kg.

TABLE 27

3-(N^4-METHYLPIPERAZINOMETHYL)-1-OXO-1,2,3,4-TETRAHYDROISOQUINOLINE(108e)

TEST	DOSE mg/Kg	EFFECTS						SUMMARY
		REACTION TIMES			BEHAVIOUR			
		TEST	SALINE	REFERENCE DRUG	DEP	NORM	STIM	
Hot-plate 55°C	50 S.C.	5,15,10 $\Sigma x = 30$	9,12,15 $\Sigma x = 37$	codeine 50mg/Kg		✓		-
				30,>60,>60 $\Sigma x = 150$				
Hot-plate 59°C (interact. with morphine 15mg/Kg)	50 S.C.	10,>40, >40 $\Sigma x = 90$	8,10,11 $\Sigma x = 29$	morphine 15mg/Kg		✓		±
				all 3 >40 $\Sigma x = 120$				
				morphine + pentaz. 40mg/Kg				
				11,15,19 $\Sigma x = 45$				
Phenyl-quinone (2mg/Kg I.P.)	100 P.C.	Total number of writhes				✓		++
		TEST	WATER	CODEINE 10mg/Kg				
		51 % inhib. = 80.9	267	120 % inhib. = 55.1				
Toxicity	50 S.C.	No. dead = 0 out of 3 S.C. $LD_{50} > 50$mg/Kg						

Remarks:- a) Compound (108e) is being further investigated using the adjuvant arthritis test.

BIBLIOGRAPHY

1. C.C. Pfeiffer, Mod. Hosp., 1951, 76, 100.
2. L.F. Small, N.B. Eddy, E. Mosettig and C.K. Himmelsbach, "Studies on Drug Addiction", Suppl. No. 138, Washington, D.C., 1938.
3. K.W. Bentley, Endeavor, 1964, 23, 97.
4. J.W. Lewis, K.W. Bentley and A. Cowan, Ann. Rev. Pharmacol., 1971, 11, 241.
5. O. Eisleb and O. Schaumann, Deut. medicin. Woch., 1939, 65, 967.
6. A.D. Macdonald, G. Woolfe, F. Bergel, A.L. Morrison and H. Rinderknecht, Brit. J. Pharmacol., 1946, 1, 4.
7. a) W.D. Avison and A.L. Morrison, J. Chem. Soc., 1950, 1469.
   b) H. Kägi and K. Miescher, Helv. Chim. Acta, 1949, 32, 2489.
8. K.A. Jensen, F. Lindquist, E. Rekling and C.G. Wolfbrandt, Dansk. Tidssk. Farm., 1943, 17, 173.
9. a) T.D. Perrine and N.B. Eddy, J. Org. Chem., 1956, 21, 125.
   b) T.D. Perrine and N.B. Eddy, J. Chem. Soc., 1944, 269.
10. P.A.J. Janssen, Chem. Abs., 1964, 61, 10689.
11. P.A.J. Janssen and A.H. Jageneau, J. Pharm. Pharmacol., 1957, 9, 381.
12. D.W. Adamson and A.F. Green, Nature, 1950, 165, 122.
13. R. Grewe, Naturwissenschaften, 1946, 33, 333.
14. E.L. May and J.G. Murphy, J. Org. Chem., 1955, 20, 257.
15. A. Hunger, J. Kebrle, A. Rossi and K. Hoffman, Experientia, 1957, 13, 400.
16. G. de Stevens, ed., "Analgetics", Academic Press, New York, London, 1965, chap. 8.
17. A.H. Beckett, J.Pharm. Pharmacol., 1952, 4, 425.
18. A.H. Beckett and A.F. Casy, J. Pharm. Pharmacol., 1954, 6, 986.

19. O.J. Braenden, N.B. Eddy and H. Halbach, Bull. Wld. Hlth. Org., 1955, 13, 937.

20.a) A.H. Beckett, J. Pharm. Pharmacol., 1956, 8, 848.

b) A.H. Beckett, A.F. Casy, N.J. Harper and P.M. Phillips, J. Pharm. Pharmacol., 1956, 8, 860.

21. N.P. Eddy, Chem. and Ind., 1959, 47, 1462.

22. P.A.J. Janssen, Brit. J. Anaesthesia, 1962, 34, 260.

23. P.S. Portoghese, J. Med. Chem., 1965, 8, 609.

24. H.G. Mautner, Ann. Rep. Med. Chem., 1968, 230.

25. G.C.R. Roberts and O. Jardetzky, Advan. Protein Chem., 1970, 24, 447.

26. A. Goldstein, Life Sciences 1974, 14, 615.

27. E. Overton, "Studien uber die Narkose", G. Fischer, Jena, 1901.

28. H. Meyer, Arch. Exp. Pathol. Pharmacol., 1899, 42, 109.

29. J. Ferguson, Proc. Roy. Soc., 1939, 127B, 387.

30. L.P. Hammett, "Physical Organic Chemistry", McGraw-Hill, New York, London, 1940, p186.

31. O.R. Hansen, Acta Chem. Scand., 1962, 16, 1593.

32. R. Zahradnik, Arch. Int. Pharmacodyn., 1962, 135, 311.

33. S.M. Free and J.W. Wilson, J. Med. Chem., 1964, 7, 395.

34. J.A. Singer and W.J. Purcell, J. Med. Chem., 1967, 10, 1000.

35. C Hansch, R.M. Muir, T. Fujita, P.P. Maloney, F. Geiger and M. Streich, J. Am. Chem. Soc., 1963, 85, 2817.

36. T. Fujita, J. Iwasa and C. Hansch, J. Am. Chem. Soc., 1964, 86, 5175.

37. J. Iwasa, T. Fujita and C. Hansch, J. Med. Chem., 1965, 8, 150.

38. C. Hansch, A.R. Steward and J. Iwasa, Mol. Pharmacol., 1965, 1, 87.

39. C. Hansch, A.R. Steward, J. Iwasa and E.W. Deutsch, Mol.

Pharmacol., 1965, 1, 205.

40. C. Hansch, E.W. Deutsch, and R.N. Smith, J. Am. Chem. Soc., 1965, 87, 2738.

41. C. Hansch, A.R. Steward, S.M. Anderson and D. Bailey, J. Med. Chem., 1968, 11, 1.

42. C. Hansch, E.J. Lien and F. Helmer, Arch. Biochem. Biophys., 1968, 128, 319.

43. C. Hansch, Acc. Chem. Res., 1969, 2, 232.

44. J. T. Penniston, L. Beckett, D.L. Bentley and C. Hansch, Mol. Pharmacol., 1969, 5, 333.

45. T. Higuchi and S.S. Davies, J. Pharm. Sci., 1970, 59, 1376.

46. B. Hermans, P. Van Daele, C. Van de Westeringh, C. Van Der Eycken, J. Boey and P.A.J. Janssen, J. Med. Chem., 1965, 8, 851.

47. C. Van de Westeringh, P. Van Daele, B. Hermans, C. Van Der Eycken, J. Boey and P.A.J. Janssen, J. Med. Chem., 1964, 7, 619.

48. J. Weiljard, P.D. Oratrovats, A.F. Sullivan Jr., G. Purdue, F.K. Heath and K. Pfister 3rd., J. Am. Chem. Soc., 1956, 78, 2342.

49. B. Elpern, P. Carabateas, A.E. Soria, C.N. Gardner and L. Grumbach, J. Am. Chem. Soc., 1959, 81, 3784.

50. N. Itoh, Chem. Pharm. Bull., 1962, 10, 55.

51. G.B.A. Veitch, Ph.D. Thesis, University of Aston in Birmingham, 1971.

52. Y. Ogata and A. Kawasaki, J. Chem. Soc.(B), 1971, 325.

53. S. Patai, ed., "The Chemistry of the Amino Group", Interscience, London, 1968, p283.

54. E. Honkanen, Ann. Acad. Sci. Fennicae Ser. IIA, 1960, 99, 80pp Chem. Abs., 1961, 55, 15401h.

55. Laaketehdas Orion Oy., B.P. 877,846/1960.

56. Laaketehdas Orion Oy., B.P. 896,720/1962.

57. B. Luning, Acta Chem. Scand., 1959, 13, 1623.

58. G. Tsatsas, E. Costakis, J.F. Zaroslinski, R.K. Browne and L.H. Possley, J. Med. Chem., 1970, 12, 870.

59. F. Takenaka, Japan J. Pharmacol., 1959, 9, 55.

60. A.A. Aroyan, R. Sh. Arshakyan and T.R. Ovsepyan, Izv. Akad. Nauk. Arm. SSR. Khim. Nauki, 1963, 16, 277.

61. R.B. Moffat, J. Med. Chem., 1964, 7, 319.

62. L. Vargha, G. Kasztreiner, J. Borsy, L. Farkas, J. Kuszmann and B. Dumbovich, Biochem. Pharmacol., 1962, 11, 639.

63. G. Kasztreiner, J. Borsy and L. Vargha, Biochem. Pharmacol., 1962, 11, 651.

64. G.A. Starmer, S. McClean and J. Thomas, Toxicol. Appl. Pharmacol., 1971, 19, 20.

65. C. Hansch, P.P. Maloney and T. Fujita, Nature, 1962, 194, 178.

66. C. Hansch and A.R. Steward, J. Med. Chem., 1964, 7, 691.

67. C. Hansch and T. Fujita, J. Am. Chem. Soc., 1964, 86, 1616.

68. T. Fujita and C. Hansch, J. Med. Chem., 1967, 10, 991.

69. P.S. Portoghese, J. Pharm. Sci., 1965, 54, 1077.

70. A. Cammarata and R.C. Allen, J. Pharm. Sci., 1967, 56, 640.

71. R.H. Sarma and C.L. Woronick, Biochemistry, 1972, 11, 170.

72. F.W. Oberst and H.L. Andrews, J. Pharmacol. Exp. Therap., 1941, 71, 38.

73. A. Albert and G.P. Serjeant in "Ionisation Constants of Acids and Bases", Methuen, London, 1962.

74. S-Y. Hong, Y-T. Park and W-H. Choi, Daehan Hwahak Hwoejee, 1972, 17, 193. Chem. Abs., 1973, 79, 52622.

75. C. Hansch and S.M. Anderson, J. Med. Chem., 1967, 10, 745.

76. C. Hansch and E.J. Lien, J. Med. Chem., 1971, 14, 653.

77. E.J. Lien, C. Hansch and S.M. Anderson, J. Med. Chem., 1968, 11, 430.

78. J.C. Dearden and E. Tomlinson, J. Pharm. Pharmacol., 1971, 23(Suppl.), 73.

79. C. Hansch and S.M. Anderson, J. Org. Chem., 1967, 32, 2583.

80. S. Patai, ed., "The Chemistry of the Amino Group", Interscience, London, 1968, chap6.

81. G.A. Stein, H.A. Bronner and K. Pfister, J. Am. Chem. Soc., 1955, 77, 700.

82. H.T. Bucherer and W. Steiner, J. Prakt. Chem., 1934, 140, 291.

83. T.N. Ghosh and B. Bhattacharya, J. Ind. Chem. Soc., 1957, 34, 863.

84. E. Späth and A. Dobrowsky, Ber., 1925, 58, 1274.

85. A. McCoubrey and D.W. Mathieson, J. Chem. Soc., 1949, 696.

86. A. Pictet and T. Spengler, Ber., 1911, 44, 2030.

87. A. Albert and J.N. Phillips, J. Chem. Soc., 1956, 1294.

88. S.F. Mason, J. Chem. Soc., 1957, 4874.

89. S. Allisson, J. Büchi and W. Michaelis, Helv. Chim. Acta, 1966, 49, 891.

90. J. Büchi and S. Allisson, private communication.

91. E. Oliveri-Mandala, Gazzetta, 1925, 55, 271.

92. J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", McGraw-Hill, 1968.

93. R.H. Harradence and F. Lions, J. Proc. Roy. Soc. N. S. Wales, 1938, 72, 284.

94. Ciba Pharmaceutical Products Inc., U.S. Patent, 2,785,159, Mar. 12, 1957.

95. K. Hoffmann and H. Schellenberg, Helv. Chim. Acta, 1944, 27, 1782.

96. P.A.S. Smith and J.P. Horowitz, J. Am. Chem. Soc., 1950, 72, 3718.

97. S. Minami, M. Tomita, H. Takamatsu and S. Uyeo, Chem. Pharm. Bull., 1965, 13, 1084.

98. R. Huisgen, Ann. Chem., 1951, 574, 171.

99. P.A.S. Smith and W.L. Berry, J. Org. Chem., 1961, 26, 27.

100. J.B. Thomson, P. Brown and C. Djerassi, J. Am. Chem. Soc., 1966, 88, 4049.

101. C.P. Lewis, Anal. Chem., 1964, 36, 176.

102. C.P. Lewis, Anal. Chem., 1964, 36, 1582.

103. A. Kubo, S-I. Sakai, S. Yamada, I. Yokoe and C. Kaneko, Chem. Pharm. Bull., 1968, 16, 1533.